

REMARKS

I. Claims in th Case

Claims 1-16, 30-33 and 37-40 have b en amended.

Claims 17-29, 34-36 and 41-70 are withdrawn as being drawn to non-elected inventions.

Claim 71 has been added.

Claims 1-16, 30-33, 37-40 and 71 are presently in the case.

II. The Invention

The present invention is directed to overcome at least some of the disadvantages of the prior art by providing a bacterial gene (opd) of known DNA sequence including the translation initiation codon and which sequence encodes an organophosphorus anhydrase capable of hydrolyzing a wide spectrum of neurotoxins ranging from insecticides to mammalian neurotoxins. By virtue of the known sequence and start site of the opd gene provided by the invention, the cloned gene has been expressed in a number of hosts by the inventors. The novel approaches to expression used by the inventors led to the isolation of the membrane-associated enzyme allowing the purified enzyme to be characterized. These advances have led to a number of interrelated uses for the cloned gene and the recombinant enzyme including: potential commercial-scale detoxification of organophosphorus compounds; detection of organophosphorus compounds; protection of susceptible organisms from organophosphorus poisoning; biologically efficacious design of pesticide formulations; and, detection of organophosphorus-detoxifying microorganisms.

In order to achieve the substantial advances of the invention, the present inventors had to overcome, and invent around, a series of intractable roadblocks. To begin with, the only source of the enzymatic activity known when the inventors began their research were two soil bacteria. Neither of these bacteria are amenable to the standard laboratory techniques for growth (see, e.g., specification p. 5, lines 4-5). Moreover, no means was readily available for selecting among those colonies of bacteria which possessed the activity -- there was no minimal medium developed for

their growth and neither strain was capable of using any organophosphorus compound as a nutrient (see, e.g., specification p. 4, lines 23-26).

Standard laboratory procedures for isolating the DNA of these soil bacteria were unsuccessful and, in particular, the large plasmid DNA of these bacteria turned out to be very difficult to isolate in a condition in which it was useful (see, e.g., specification p. 4 lines 32-34). Even after the inventors developed successful techniques for the isolation of the plasmid DNA from these soil microbes, considerable designing of experiments was required in order to produce successful expression hook-ups -- a fact strengthened in its relevance by the previous failure of the inventors as well as several other groups to achieve acceptable levels of expression in any but the original strains.

One of the most difficult of the roadblocks which the inventors had to overcome involved accurate sequencing of the DNA from these soil bacteria. This procedure proved to be exceedingly difficult due to the high ratio of G-C to A-T in these particular strains (one of the highest such ratios known in bacteria).

Even more difficult for the inventors was the task of producing enough of the membrane-associated enzyme in order to purify and characterize it (see, e.g., specification p. 5, lines 1-3, 5-7). Until this was achieved, there was no way in which to verify the actual coding sequence for the enzyme and thus no way to accurately design hook-ups which allowed for expression in the variety of hosts (see, e.g., specification p. 8, lines 28-32). This was especially true since this enzyme is most likely cleaved of an N-terminal signal sequence prior to insertion in the native host bacterial cell membrane. Thus, only by virtue of the knowledge gained in the successful expression of the bacterial enzyme and knowledge of its complete sequence were the inventors able to design vectors for use with a eukaryotic expression host. It is noteworthy in this regard to observe that although minor modifications to the sequence have been made by the inventors and others since the present patent application was filed, there has been no scholarly disagreement

concerning the originally identified N-terminal sequence of the opd gene.

The inventors and others failed in achieving the quantities of enzyme necessary for substantial testing or use of the enzyme from the native bacterial sources (see, e.g., specification p. 8, lines 34-36 through p. 10, lines 1-9). High level expression of the enzyme behind promoters known in bacteria to produce large amounts of other enzymes did not prove suitable. Likewise, there was no way of knowing whether the membrane-associated enzyme from soil bacteria would be expressed to any useful degree by eukaryotic host cells. Surprisingly, however, manifold levels of enzyme were produced allowing for the purification and characterization of the enzyme by specialized eukaryotic cells selected by the inventors which had alluded the inventors and others for years (see, e.g., specification p. 10, lines 11-19).

Once the enzyme and the gene encoding the enzyme were capable of manipulation using the sequence and techniques developed by the inventors, a wide range of uses became a possibility. Among these uses are: commercial-scale detoxification of organophosphorus compounds in vitro; detection of organophosphorus compounds; protection of susceptible organisms, including humans and beneficial insects, from organophosphorus poisoning; detection of organophosphorus-detoxifying microorganisms; environmentally-sound pesticide design and controlled detoxification; among others.

These features of the present invention are submitted to represent considerable improvements over the prior art which art was discussed in the application and some of which art is cited against the application by the Examiner. In particular, the Examiner's attention is directed to the failure in the prior art to achieve: (1) a complete, and essentially correct, DNA sequence; (2) a determination of the coding sequence and, in particular, the determination of the correct start codon and reading frame within the sequence; (3) heterologous expression of the enzyme in bacteria; (4) heterologous expression of the enzyme in eukaryotic cells; (5)

isolation of and purification of utilizable quantities of the recombinant enzyme; and (6) use of the knowledge gained by the inventors to design successful hook-ups allowing expression and transformation of multi-cellular animals.

III. Requirement to State Inventor/Dates of Invention for Each Claim

The Examiner has required Applicants, under 37 C.F.R. 1.56, to point out the inventor and invention dates of each claim not commonly owned at the time that a later invention was made. This is required in order to allow the Examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

In relevant part, 35 U.S.C. § 103 states:

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. [emphasis added]

As required by the Examiner, Applicants do hereby affirm that at all times during the making of the invention/s disclosed by this application that the subject matter of all of the various claims was commonly subject to an obligation on the part of each inventor of assignment to Texas A&M University (Recordation Date, April 27, 1989: Reel/Frame, 5082/0274). Each inventor, during the making of the invention/s of the various claims, was under said obligation to Texas A&M University at the time of making of any of the invention/s disclosed in the claims of the present application. It is submitted by the Applicants that these affirmations as to the commonly owned nature of the various claims by virtue of obligations to assign to a common entity satisfies the Applicants' obligation under 37 C.F.R. 1.56.

IV. Objection to Specification under 35 U.S.C. § 112, 1st Paragraph

A. The Examiner's Objection

The Examiner has first objected to the specification under 35 U.S.C. § 112, first paragraph, for failing to provide a reasonable written description for practicing the claimed invention. In particular, the Examiner has pointed out that the specification recites using P. diminuta and a Flavobacterium sp. (ATCC 27551) (the Examiner calls attention to Harper et al., BX, and McDaniel et al., BY) which the Examiner states set forth DNA sequences coding for opd where the organophosphorus acid anhydrase DNA set forth in Figure 1 of the specification are only partially identical. The Examiner takes the position that, from the recited examples in the specification, it is not readily apparent that the species of bacteria are any different, that the plasmids used are any different, that the isolated DNA that was sequenced was any different, or that the functionality encoded by the DNA is any different. Yet, according to the Examiner, the sequences recited in the Harper et al., McDaniel et al., Mulbry et al. and Figure 1 of the specification set forth different DNA sequences coding for what is apparently the same enzyme.

The Examiner further notes that page 21 of the specification recites using the plasmid pCMS1 (Fig. 2 of Harper et al.) and sets forth the DNA sequence (Fig. 1). The Examiner argues that this is apparently the same plasmid and DNA in the specification and the RESULTS section of the McDaniel et al. reference. The Examiner cites in support of this conclusion that fig. 4 of the McDaniel reference is identical to Fig. 2 of the present application.

In conclusion, the Examiner takes the position that there are apparently at least three different references all directed to the apparently identical genetic material where no reference indicates a sequence identity for the apparently identical genetic material. Therefore, according to the Examiner, a query is raised as to what genetic material is disclosed as having the properties of the organophosphorus anhydrase.

B. Applicants' Remarks

Applicants urge that by following the teaching of the patent application as submitted, one of ordinary skill in the art may obtain, without undue experimentation, the PstI fragment represented in Figure 1 of the patent specification. As pointed out in the specification, a source of the DNA amenable to the teachings of the present invention is deposited with the ATCC as Flavobacterium sp. ATCC No. 27551 (specification p. 7, lines 26-29). Furthermore, in order to utilize the fragment in any of the embodiments of the invention, one of skill in the art will realize that the most important sequence information provided by the specification in Figure 1 is the ATG start site identified and verified by the inventors only after considerable effort and invention. It is important to note that no modifications to the sequence which have been suggested by the inventors or others modify any portion of the region surrounding the originally identified start site which site and immediately surrounding sequence is critical in the preparation of proper hook-ups for expression of the gene. For instance, Serdar et al. (Bio/Technology 7:1151-1155 (1989)) suggests a change in the sequence of Figure 1 of the present patent application at a site no closer than 55 base pairs upstream of the start site identified by the inventors, while Mulbry et al. suggests a change at a site no closer than 35 base pairs from the same ATG start site.

Thus, it is submitted that Figure 1 of the present specification complies with 35 U.S.C. § 112, first paragraph, by providing a reasonable written description for practicing the claimed invention. This is submitted to be the case even if the sequence as shown in Figure 1 of the specification is modified to the greatest extent suggested by the inventors and others (a change of no more than approximately 2%, at most).

The Examiner's attention is also drawn to the relative publication and filing dates of the art cited on the paragraph spanning pp. 6-7 of the Office Action of May 24, 1991. The McDaniel et al. article was published in May 1988. Harper et al. was published in October 1988. The present patent application was filed

in April 1989. Two subsequent references which discuss the sequence of the opd gene were published after the filing date of the present application and do not represent prior art. Mulbry et al. (cited by the Examiner in this rejection) was published in December 1989, while Serdar et al. (cited in the Mulbry et al. reference as "in press") was published November 1989. Thus, while they are of interest for the reasons set forth below, the later two publications are not properly cited against the present application.

The Examiner correctly notes that there are differences between the sequences shown in McDaniel et al., Harper et al., Mulbry et al. and Figure 1 of the patent specification. The Examiner did not have the benefit of reviewing the non-prior art reference Serdar et al., but should he so have reviewed it he would have seen differences between this reference and each (including Mulbry et al.) of the four sequences noted above, as well. However, Applicants submit that to characterize the sequences as only partially identical is a gross misstatement. The subsequently published sequences are, by any standard of comparison, overwhelmingly identical to the sequence for the opd gene originally discovered by the inventors.³ In order to visualize how substantially identical these sequences are, the Applicants have produced a chart (Exhibit A), entitled "Comparison of opd Sequence Disclosed in Patent Application to Published Sequences." The Examiner's attention is directed to the appended Exhibit for purposes of the remaining analysis of this basis for rejection.

There are a total of 1430 bases which overlap from all of the references noted above. The sequence originally obtained by the inventors and which was published in McDaniel et al. was corrected at nine (9) positions in the subsequent publication by the inventors (Harper et al.) which correlates to a percentage difference of less than 1.0% (0.63%). The inventors had, by the time that the patent

³This conclusion is acknowledged by Serdar et al. (1989), p. 1153, second column, third paragraph: "Most of the sequence was found to be identical with that obtained by this study."

application was to be filed, corrected the sequence by an additional small increment (including corrections of corrections made in the Harper et al. sequence). The difference between the Harper et al. sequence and that in Figure 1 of the present application is again only incremental (nine [9] base changes). Therefore, the best sequence known to the inventors at the time the application was filed is shown in the patent application at Figure 1 and only differs incrementally from the sequence originally published by the inventors.

35 U.S.C. § 112 mandates the disclosure of the best mode contemplated by the inventors. That the inventors were making every attempt to meet this requirement and in fact did so meet this requirement is evident in the disclosure of the sequence in Figure 1 which is an improvement over the sequence published in both McDaniel et al. and Harper et al..⁴ This is made even more evident when comparing subsequently published sequences cited by the Examiner. Thus, by comparing the coding sequences between Figure 1 of the present application and the "corrected" sequence of Mulbry et al. (which was compared to the Harper et al. sequence only), one can readily see that twelve (12) of the alleged differences between the Harper et al. sequence and the Mulbry et al. sequence are, in fact, identical in the sequence disclosed in Figure 1 of the present application. The remaining differences between the Figure 1 coding sequence disclosed in the present application and that published by Mulbry et al. represent only approximately between 1.5%-2.1% (17/1144 or 26/1248 differences, respectively) depending upon which termination signal is correct. Furthermore, even though the Mulbry et al. authors cite the in press article of Serdar et al. as disclosing an "identical" opd gene sequence, in fact there are several differences between these sequences as well.

⁴It should be noted that:

There is no statutory basis for reading into the best-mode portion a requirement that the mode disclosed be in fact the optimum mode for carrying out the invention. *In re Bosy*, 149 U.S.P.Q. 789 (C.C.P.A. 1966).

The reason that this sequence has proven so difficult to accurately obtain is at least in part due to the relatively high G+C content of the DNA of the organisms from which this was isolated. Thus, there is a 53% (765/1430) G+C content in the PstI fragment sequenced by the inventors and others.⁵ A phenomenon termed "GC compaction" causes considerable difficulty in many of the commonly available DNA sequencing techniques giving rise to spurious G's and C's. More recently available technology, such as that more recently employed by the inventors and others, has improved the ability of the DNA sequencer to overcome problems associated with GC compaction and similar anomalies.

The Examiner's attention is drawn to the fact that the vast majority of changes between the inventor's own investigations (McDaniel et al. and Harper et al.) and Figure 1 of the present application as well as those between Figure 1 of the present application and the subsequently published sequence of Mulbry et al. are, in fact, differences which add, delete or rearrange G's and C's in the sequence. Thus, for instance, of the differences between the sequence in Harper et al. of the present application and the analogous sequence from Mulbry et al., 47 of the putative 50 differences cited by Mulbry et al. involve G's and C's. Likewise, virtually all of the differences between the sequence of Figure 1 and the sequences disclosed in the inventor's own references involve G's and C's.

While it is vastly correct in its presently disclosed form, and while it is absolutely correct (according to the best of the inventors' own results as well as the results of others) as to the critical 5' translational start site, the actual sequence outside of the critical 5' region is most likely something slightly different but between that disclosed in Figure 1 of the present application and the various sequences cited by the Examiner. In fact, this is

⁵The fact that this high G + C ratio contributes to the minor discrepancies in the published sequences is acknowledged by Serdar et al. (1989), p. 1154, column 1, last two lines.

precis ly the current best understanding of the Applicants and results in a composite sequence believed by them to be the most correct sequence . It is submitted that the Applicants, in complying with the best mode requirements in the originally filed application, provided the sequence believed by them to be the most accurate. In only a handful of minor ways, the inventors have since modified their originally filed sequence. However, for this reason, the Applicants have constructed a substitute Figure 1 which they request they be allowed to substitute for the originally filed Figure 1.⁶

In support of this substitute Figure 1 if allowed, a declaration of the inventors will be submitted as well stating that such substitute does not introduce any substantive new matter into the case since the corrected sequence is an inherent characteristic of the opd gene sequence enabled by the current invention. In so doing, Applicants submit that they will remain in full compliance with 35 U.S.C. § 112, first paragraph, by providing a reasonable written description for practicing the claimed invention.⁷ It is,

⁶Applicants do not believe they are obligated to submit the substitute Figure 1 in compliance with the new 37 C.F.R. 1.821-1.825 requirements in a computer-readable format. However, should such a submission be actually required, or should the Examiner so desire, Applicants are willing to submit the substitute sequence in compliance with the Biotechnology Invention Disclosure requirements. The Examiner is requested to contact Applicants' representative in order to inform him of the best manner in which to submit the substitute figure if allowable.

⁷It is Applicants' position that *Ex parte Marsili et al.*, 214 U.S.P.Q. 904 (PTO Bd. App. 1979) is controlling in cases where originally disclosed chemical compounds require subsequent modification. In that case, an amendment to an originally filed chemical formula changing an imidazoline ring to a imidazole ring was required. This change, while clearly altering the chemical structure originally disclosed in the specification, was held not to add new matter and to be in keeping with the PTO's mandate of promoting the progress of science. *Marsili* is in agreement with the precedent established in cases such as *In re Magerlein et al.*, 52 C.C.P.A. 1637, 346 F.2d 609, 145 U.S.P.Q. 683 (1965) and *In re Fisher*, 57 C.C.P.A. 1099, 427 F.2d 833, 166 U.S.P.Q. 18 (1970), where the courts held that a structural formula may be corrected without violation of 35 U.S.C. 132, if "there is sufficient evidence in the record to show the [proposed structure] to be an

ther fore, requested that the Examiner allow the requested substitution informing Applicants' representative how best to achieve such substitution and remove this basis for rejection from the case.

V. Rejection of Claims 2, 3, 11 and 13 Under 35 U.S.C. § 112, Second Paragraph

A. The Examiner's Rejection

The Examiner has rejected claims 2, 3, 11 and 13 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner takes the positions:

- (1) that the terminology "extraneous DNA" in claim 2 is vague and indefinite;
- (2) that the DNA referred to in claim 3 is not clearly indicated as being a plasmid or isolated DNA as from a naturally occurring plasmid;
- (3) that claim 11 is vague and indefinite in reciting "capable" which is only latent capacity; and
- (4) that claim 13 is vague and indefinite with regard to the terms "microorganism" and "bacteria", in particular, with regard to the plural discontinuity.

B. Applicants' Remarks

Applicants have amended the claims in a manner which is submitted to overcome the rejections cited by the Examiner under 35 U.S.C. § 112, second paragraph. Thus, claims 2, 3, 11 and 13 have each been amended as follows.

In the amended claim 2, the gene fragment of claim 1 is limited further as being a fragment substantially free of DNA in a direction

inherent characteristic of the subject matter so identified." *In re Magerlein et al.*, 52 C.C.P.A. at 1640.

5', or upstream, of the start codon which intervening DNA may interfere with the expression of the gene. In amended claim 3, the DNA sequence of claim 1 is specifically described as being the DNA sequence of claim 1 as it is incorporated into a recombinant plasmid. Claim 11 as amended describes a vector further comprising a Drosophila transposon, implying thereby the capability of the transposon to transpose the fruitfly genome. Claim 13 as amended corrects the improper plurals by deleting the word "bacteria" and replacing it with the word "bacterium".

Applicants submit that these amendments fully and completely overcome the rejection and request that such rejection be removed from the case.

VI. Rejection of Claims 7-10 and 30-33 Under 35 U.S.C. § 112, Fourth Paragraph

A. The Examiner's Rejection

The Examiner has also rejected claims 7-10 and 30-33 under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. Particularly, the Examiner takes the position that the expression vector of claim 6 implicitly must have present a promoter, start signal, and termination codons in the proper reading frame in order for the heterologous DNA to be expressed. Thus, the Examiner argues, claims 7-10 do not further limit claim 6.

As to claims 30-33, the Examiner takes the position that these claims do not further limit the claims (1, 6, 12 and 14, respectively) from which they depend since there is no sequence shown in the independent claims which can be deleted. The Examiner notes that the DNA and amino acid sequences already start with ATG and methionine, respectively.

B. Applicants' Remarks

Rejected claims 7-10 and 30-33 have been amended in view of the above rejections. Claim 6 as amended describes a generic vector for producing bacterial organophosphorus acid anhydrase where the vector comprises a recombinant bacterial organophosphorus acid anhydrase gene further comprising the DNA sequence shown in Figure 1. Thus, amended claims 7-10 now properly further limit the vector of claim 6 by describing specific vectors. Claim 7 as amended describes an expression vector with a specific hook-up. The claims 8-10 depending from claim 7 further limit the claim to expression vectors derived from a baculovirus, vectors comprising bacteriophage and vectors comprising plasmids.

Claims 30-33 depend from claims 1, 6, 12 and 14, respectively. Both the independent and dependent claims have been amended. In particular, the dependent claims 30-33 have been amended to more clearly indicate the sequence which may be deleted. In particular, each of the rejected claims 30-33 has been amended to show that it is possible to delete a portion of the DNA sequence 5' of the start codon from the DNA sequence depicted in Figure 1.

The Examiner is certainly correct in pointing out that the determination of the ATG start codon has already been made and is present in the sequence taught by the present application. In fact, it is this very information which the invention teaches as necessary for one of skill in the art to carry out further modifications of the sequence shown in Figure 1 in order to alter the 5' sequence outside of the coding region of the opd gene.

It is submitted by the Applicants that these amendments and the arguments above fully overcome the Examiner's rejections. It is requested that the rejections, therefore, be removed.

VII. Rejection of Claims 1-3, 5-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 102(a) Over McDaniel et al. (BY)

A. The Examiner's Rejection

The Examiner has rejected claims 1-3, 5-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 102(a) as being anticipated by McDaniel et al. (BY). The Examiner takes the position that McDaniel et al. discloses cloning and expression of an opd gene encoding a phosphotriesterase using the same strains, vectors, restriction enzymes and DNA fragment. The Examiner further notes the unexplained disparity of the sequences noted previously and concludes that the DNA sequences are the same.

The Examiner also takes the position that this same reference forms the basis for a rejection under 35 U.S.C. § 103. This rejection will be treated separately below.

B. Applicants' Remarks

McDaniel et al. does not qualify as 35 U.S.C. § 102(a) prior art.

The Examiner's attention is again drawn to the relative publication and filing dates of the art cited. The McDaniel et al. article was published in May 1988. The present patent application was filed in April 1989.

MPEP 715.01(c) states:

Where the applicant is one of the co-authors of a publication cited against his application, he is not required to file an affidavit or declaration under 37 C.F.R. 1.131. The publication may be removed as a reference by filing a disclaiming affidavit or declaration of the other authors. *Ex parte Hirschler*, 110 U.S.P.Q. 384.

However, a co-author's disclaiming affidavit is apparently not necessarily required. In *In re Katz*, 687 F.2d 450, 215 U.S.P.Q. 14 (CCPA 1982), the Court held that disclaiming affidavits were not necessary. The Court clearly stated that authorship does not give rise to any presumption regarding inventorship. The only requirement appears to be a "reasonable showing supporting the basis for the applicant's position." 215 U.S.P.Q. at 18. The Examiner,

under this case law, is not free to speculate about the alternatives in the face of the applicant's own sworn satisfactory explanation. See, *In re Kusko*, 215 U.S.P.Q. 972 (PTO Bd. App. 1981) (reaching the same opinion).

The Declaration of Invention filed in conjunction with the present application is submitted by Applicants to be in accord with the relevant case law cited above in providing a "sworn satisfactory explanation" of the inventorship of the present application.⁸ The reference McDaniel et al. was co-authored by McDaniel, Harper and Wild. The reference Harper et al. was co-authored by Harper, McDaniel, Miller and Wild. Co-inventor Raushel was not an author on either of these articles. The additional co-authors of both the McDaniel et al. and Harper et al. references were either technicians (Harper) or students (Miller) working in conjunction with the inventors in order to reduce the inventions of McDaniel, Wild and Raushel to practice.

It is believed by the Applicants that this further explanation in combination with the originally filed sworn Declaration of Inventorship is sufficient to fully overcome the rejection under 35 U.S.C. § 102(a) cited against the application in view of cases such as *In re Katz*. However, should the Examiner so require, a disclaiming affidavit from both Harper and Miller will be obtained and submitted.

⁸The relevant portion of the Declaration sworn to by each of the three inventors of the present application and filed therewith in the Patent and Trademark Office states:

I believe I am the original, first and sole inventor (if only one name is listed below) or the below named inventors are the original, first and joint inventors (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled RECOMBINANT ORGANO-PHOSPHORUS ACID ANHYDRASE AND METHODS OF USE the specification of which is attached hereto.

VIII. Rejection of Claims 1-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 102(a) Over Harper et al.

A. The Examiner's Rejection

The Examiner has rejected claims 1-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 102(a) as being anticipated by Harper et al. (BY). Similarly to the rejection stated for McDaniel et al. above, the Examiner takes the position that McDaniel et al. discloses cloning and expression of an opd gene encoding a phosphotriesterase where the DNA sequence is the same for p. diminuta and a Flavobacterium sp. (ATCC 27551). The Examiner again notes that the same strains, vectors, restriction enzymes and DNA fragment disclosed in the reference are used in the patent application. The Examiner again further notes the unexplained disparity of the sequences noted previously and concludes that the DNA sequences are the same.

The Examiner also takes the position that this same reference forms the basis for a rejection under 35 U.S.C. § 103. This rejection will be treated separately below.

B. Applicants' Remarks

Harper et al. does not qualify as 35 U.S.C. § 102(a) prior art.

The Examiner's attention is again drawn to the relative publication and filing dates of the art cited. Harper et al. was published in October 1988. The present patent application was filed in April 1989.

As noted above, the same arguments apply as an explanation of the authorship and inventorship of the McDaniel et al. and Harper et al. publications. It is believed by the Applicants, as argued above, that this statement is sufficient to fully overcome the rejection under 35 U.S.C. § 102(a) cited against the application in view of cases such as *In re Katz*. However, should the Examiner so require, a disclaiming affidavit from both Harper and Miller will be obtained and submitted.

IX. Rejection of Claims 1-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 102(b) as Anticipated by Wild (AT) or Mulbry (AY)

A. The Examiner's Rejection

The Examiner has rejected claims 1-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 102(b) as being anticipated by Wild et al. (AT) or Mulbry et al. (AY). The Examiner takes the position that Wild et al. discloses cloning and expression of organophosphorus degrading genes from P. diminuta and a Flavobacterium and that Mulbry et al. discloses cloning and expression of organophosphorus genes from P. diminuta and a Flavobacterium (ATCC 27551) using a cloned DNA fragment that contained the opd gene derived from P. diminuta. The Examiner additionally takes the position that while the DNA sequence is not disclosed in either of the references, that only "routine sequencing would have been needed to determine the sequence."

The Examiner also takes the position that this same reference forms the basis for a rejection under 35 U.S.C. § 103. This rejection will be treated separately below.

B. Applicants' Remarks

1. Wild et al. does not teach the DNA sequence of the opd gene nor does it anticipate the difficulty that the present inventors encountered in obtaining the sequence and the initiation codon necessary for subsequent manipulation of the opd gene for purposes of the critical expression of the gene.

The Examiner's attention is drawn to the fact that the Wild reference does not teach where the open reading frame occurs within the originally isolated fragment from the soil bacteria. In fact, the Wild reference teaches that it is possible to enhance expression of the opd gene product by removing approximately 250 base pairs of DNA from the 5' flanking sequence of the fragment. To the contrary, the present invention teaches that removal of such a region of DNA from the opd gene-containing fragment eliminates any OPA activity (see, Fig. 2). Thus, if one were to follow the teachings of the Wild reference, one would place the initiation site of the opd gene at least 250 base pairs downstream of the PstI site and

approximately at least 190 base pairs away from the actual initiation site. In fact, were one to make such a construction by deleting the first 250 base pairs from the PstI fragment, one would throw away the fragment containing the actual initiation site. What the disclosures of the Wild reference reiterates, in fact, is the confused state of the art prior to the present invention.

Thus, while there are some similarities between the elements of the present invention and the Wild reference, the critical discoveries which allowed the inventors and others to successfully clone, sequence, and express high levels of opd gene product had to await the inventions described in the present application. For these reasons, the Applicants submit that the Wild reference is improperly cited by the Examiner as a barring reference under 102(a). It is, therefore, requested that this basis of rejection be removed from the case.

2. Mulbry et al. also does not teach the DNA sequence of the opd gene nor does it anticipate the difficulty that the present inventors encountered in obtaining the sequence and the initiation codon necessary for subsequent manipulation of the opd gene for purposes of the critical expression of the gene.

Mulbry et al. is a reference which represents a collaboration between the inventors and certain scientists at the U.S.D.A. to expand the U.S.D.A.'s results in cloning to the bacterium Flavobacterium. Again, as in the previously discussed reference, the Mulbry et al. reference does not teach the DNA sequence of the opd gene nor does it anticipate the difficulty that the present inventors encountered in obtaining the sequence and the initiation codon necessary for subsequent manipulation of the opd gene for purposes of the critical expression of the gene. Thus, the same arguments addressed above apply equally well to Mulbry et al.

Thus again, while there are some similarities between the elements of the present invention and the Mulbry reference, the critical discoveries which allowed the inventors and others to successfully clone, sequence, and express high levels of opd gene

product had to await the inventions described in the present application. For these reasons, the Applicants submit that the Mulbry reference is also improperly cited by the Examiner as a barring reference under 102(a). It is, therefore, requested that this basis of rejection be removed from the case.

X. Rejection of Claims 1-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 102(b) as Anticipated By McDaniel (AZ)

A. The Examiner's Rejection

The Examiner has rejected claims 1-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 102(b) as being anticipated by McDaniel (AZ). The Examiner takes the position that the McDaniel reference discloses cloning and expression of an opd gene encoding a phosphotriesterase using the same strains, vectors, restriction enzymes and DNA fragment as the present invention disclosure. The Examiner in particular notes at least page iii, the tables, page 46, 55-56, 69, figures 17 and 19, pages 82, 89-91 and 116-120. The Examiner correctly points out that although sequencing was performed, there was no disclosure of the sequence in the reference.

The Examiner also takes the position that this same reference forms the basis for a rejection under 35 U.S.C. § 103. This rejection will be treated separately below.

B. Applicants' Remarks

The McDaniel reference (AZ) represents a Ph.D. dissertation of one of the inventors. It was preliminary in nature as to the studies which were ultimately to give rise to the inventions of the present application. Clear evidence of the preliminary nature of this reference is the fact that the DNA sequence of the opd gene is not disclosed herein although attempts to obtain such a sequence were clearly carried out as shown in the reference at the points recognized by the Examiner. The inventors were unable at the time of the publication of this reference to even provide preliminary sequencing information since the difficulties heretofore described

prevent d them from accurate sequencing.

Thus, while the McDaniel reference does give an indication of r search in progress which led to the inv ntion, it clearly does not teach one of skill in the art how to make the invention. In fact, the McDaniel reference teaches away from the current invention in important ways. For these reasons, Applicants submit that the McDaniel reference does not anticipate the present invention and should, therefore, be removed as a basis for rejection of the claims.

XI. Rejection of Claims 1-3, 5-7, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 102(b) as Anticipated By Serdar et al. (BC)

A. The Examiner's Rejection

The Examiner has rejected claims 1-3, 5-7, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 102(b) as being anticipated by Serdar et al. (BC). The Examiner takes the position that the Serdar reference discloses cloning and expression of a gene encoding a parathion hydrolase from pCMS1 into pBR322 in E. coli using at least enzymes PstI and BamHI to obtain a DNA fragment. The Examiner concludes that this reference, therefore, anticipates the present invention.

The Examiner also takes the position that this same reference forms the basis for a rejection under 35 U.S.C. § 103. This rejection will be treated separately below.

B. Applicants' Remarks

The Serdar reference is another preliminary reference which was indicative of the state of the art around the time of the McDaniel (AZ) reference discussed immediately above. The Examiner's attention is again drawn to the fact that no sequence information is provided in the Serdar reference. These authors did not publish sequence information on this gene until 1989 (June 1985 until

November 1989 - a period of over 4 years).⁹ Applicants submit that this is yet another indication of the difficulty encountered by the present inventors as well as others in obtaining the accurate sequence and the accurate start site for the gene which produces this membrane-associated enzyme in these soil bacteria.

It is submitted, therefore, that the Serdar reference does not anticipate the present invention. It is requested that the Examiner remove the rejections under 35 U.S.C. § 102(b) as barring patentability of the application.

XII. Rejection of Claims Under 35 U.S.C. § 103

A. The Examiner's Rejections

1. 35 U.S.C. § 103 Rejections made in combination with 35 U.S.C. § 102(a) Rejections Addressed Above
 - a. Rejection of Claims 1-3, 5-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 103 Over McDaniel (BY)

The Examiner has also rejected claims 1-3, 5-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 103 as being obvious over McDaniel et al. (BY). The Examiner takes the position that McDaniel et al. discloses cloning and expression of an opd gene encoding a phosphotriesterase using the same strains, vectors, restriction enzymes and DNA fragment. The Examiner further notes the unexplained disparity of the sequences noted previously.

- b. Rejection of Claims 1-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 103 Over Harper et al.

The Examiner has also rejected claims 1-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 103 as being obvious over Harper et al. (BY). Similarly to the rejection stated for McDaniel et al. above, the Examiner takes the position that Harper et al. discloses cloning

⁹Even when these authors did publish sequence information concerning the opd gene, they did so well after the information was made public by the inventors' disclosure in May of 1988.

and expression of an opd gene encoding a phosphotriesterase where the DNA sequence is the same for P. diminuta and a Flavobacterium sp. (ATCC 27551). The Examiner notes that the same strains, vectors, restriction enzymes and DNA fragment disclosed in the reference are used in the patent application and further notes the unexplained disparity of the sequences noted previously concluding that the DNA sequences are the same.

**2. 35 U.S.C. § 103 Rejections made in combination with
35 U.S.C. § 102(b) Rejections Addressed Above**

**a. Rejection of Claims 1-7, 9, 10, 12-13, 30-32
and 37-39 under 35 U.S.C. § 103 as Obvious Over
Wild (AT) or Mulbry (AY)**

The Examiner has rejected claims 1-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 103 as being obvious over Wild et al. (AT) or Mulbry et al. (AY). The Examiner takes the position that Wild et al. discloses cloning and expression of organophosphorus degrading genes from P. diminuta and a Flavobacterium and that Mulbry et al. discloses cloning and expression of organophosphorus genes from P. diminuta and a Flavobacterium (ATCC 27551) using a cloned DNA fragment that contained the opd gene derived from P. diminuta. The Examiner takes the position that while the DNA sequence is not disclosed in either of the references, that only "routine sequencing would have been needed to determine the sequence."

**b. Rejection of Claims 1-7, 9, 10, 12-13, 30-32
and 37-39 under 35 U.S.C. § 103 Over McDaniel
(AZ)**

The Examiner has rejected claims 1-7, 9, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 103 as being obvious over McDaniel (AZ). The Examiner takes the position that the McDaniel reference discloses cloning and expression of an opd gene encoding a phosphotriesterase using the same strains, vectors, restriction enzymes and DNA fragment as the present invention disclosure.

c. Rejection of Claims 1-3, 5-7, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 103 as Obvious over Serdar (BC)

The Examiner has rejected claims 1-3, 5-7, 10, 12-13, 30-32 and 37-39 under 35 U.S.C. § 103 as being obvious over Serdar et al. (BC). The Examiner takes the position that the Serdar reference discloses cloning and expression of a gene encoding a parathion hydrolase from pCMS1 into pBR322 in E. coli using at least enzymes PstI and BamHI to obtain a DNA fragment.

3. Independent Rejections Based on 35 U.S.C. § 103

a. Rejection of Claims 1-10, 12-16, 30-33 and 37-40 Under 35 U.S.C. § 103 as unpatentable over Luckow et al. taken with all of Wild et al. (AT), Mulbry et al. (AY), McDaniel (AZ), and Serdar et al. (BC).

The Examiner has also rejected claims 1-10, 12-16, 30-33 and 37-40 under 35 U.S.C. § 103 as unpatentable over Luckow et al. taken with all of Wild et al. (AT), Mulbry et al. (AY), McDaniel (AZ), and Serdar et al. (BC). The Examiner takes the position that Luckow discloses that foreign genes are readily expressed using baculovirus vectors and that such vectors are widely accepted for expression of proteins of agricultural and medical importance. The Examiner suggests that one of ordinary skill in the art would have been motivated to use baculovirus vectors and hosts because the heterologous products produced are biologically active and produce recombinant products very similar to the authentic proteins. The Examiner notes further that such vectors may be used to in expressing prokaryotic or eukaryotic genes in order to obtain abundant expression of recombinant proteins. The Examiner correctly notes that Luckow does not disclose an organophosphorus acid anhydase DNA. However, the Examiner concludes that the combination of Luckow with all of the references cited (Wild, Mulbry, McDaniel and Serdar) would have resulted in DNA coding for the organophosphorus acid anhydase inserted in the appropriate baculoviral and/or bacterial vectors and transformed host cells. Thus, the Examiner finally concludes that the invention was, as a

whole, clearly prima facie obvious in absence of evidence to the contrary.

- b. Rejection of Claims 1-16, 30-33 and 37-40 Under 35 U.S.C. § 103 As Unpatentable Over Luckow et al. Taken With All of Wild et al. (AT), Mulbry et al. (AY), McDaniel (AZ), and Serdar et al. (BC) As Applied To Claims 1-10, 12-16, 30-33 and 37-40 As Above And Further In View of Old et al.

The Examiner has also rejected claims 1-16, 30-33 and 37-40 under 35 U.S.C. § 103 as unpatentable over Luckow et al. taken with all of Wild et al. (AT), Mulbry et al. (AY), McDaniel (AZ), and Serdar et al. (BC) as applied to claims 1-10, 12-16, 30-33 and 37-40 as above and further in view of Old et al. The Examiner takes the position that the Old reference discloses that transposons are broad host range vectors whereby any cloned DNA may be introduced into Drosophila using transposable P-elements. The Examiner suggests that the teaching of the Old reference would have motivated one of ordinary skill in the art to use P-elements in Drosophila as an alternative system to the baculovirus set forth in the Luckow reference. The Examiner concludes that the combined teachings of the Luckow, Wild, Mulbry, McDaniel and Serdar references would have motivated one of skill in the art to broaden the host range of the modified vectors to include Drosophila using the teachings of the Old reference. Thus, concludes the Examiner, in absence of evidence to the contrary, the invention is prima facie obvious.

B. Applicants' Remarks

It is respectfully submitted that the foregoing references, alone or in combination, fail to teach or even to suggest any of Applicants' invention, but in particular fail to teach or even to suggest the steps necessary to accurately sequence the opd gene, to obtain the necessary information to determine the start site of the gene, which knowledge is absolutely necessary in order to modify the DNA in a manner to allow commercial scale heterologous expression of the OPA enzyme and which knowledge is absolutely necessary to obtain

heterologous expression of the membrane-associated enzyme from soil bacteria in eukaryotic systems. The proper context for determining the issue of obviousness or nonobviousness is the Supreme Court's decision in Graham v. John Deere, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) that sets forth the following considerations:

- (1) The scope and content of the prior art;
- (2) The differences between the prior art and the claims at issue;
- (3) The level of ordinary skill in the pertinent art; and
- (4) Secondary considerations such as commercial success, long-felt and unresolved needs, failures of others, etc.

See MPEP §§ 706.

1. Scope and Content of the Prior Art

a. McDaniel et al. Does Not Qualify As
35 U.S.C. § 103 Prior Art

The Examiner's attention is again drawn to the Applicants' arguments above relating to removal of this reference as a publication bar to the patentability of the present application. It is believed by the Applicants that the arguments above are similarly sufficient to fully overcome the rejection under 35 U.S.C. § 103 cited against the application in view of cases such as *In re Katz*. However, Applicants wish to reiterate that should the Examiner so require, a disclaiming affidavit from both Harper and Miller will be obtained and submitted.

b. Harper et al. Does Not Qualify As 35 U.S.C. §
103 Prior Art

The Examiner's attention is drawn to the arguments addressed in "a." above. It is believed by the Applicants, as argued above, that these arguments are sufficient to fully overcome the rejection under 35 U.S.C. § 103 cited against the application in view of cases such as *In re Katz*. However, should the Examiner so require, a

disclaiming affidavit from both Harper and Miller will be obtained and submitted.

- c. Wild et al.: (1) does not teach the DNA sequence of the opd gene; (2) does not anticipate the difficulty that the present inventors encountered in obtaining the sequence and the initiation codon necessary for subsequent manipulation of the opd gene for purposes of the critical expression of the gene; (3) does not teach means for overcoming any of the difficulties encountered by the Applicants; and (4) does clearly teach away from the present invention. Moreover, there is nothing in Wild et al. which suggests the combinations proposed by the Examiner.

As was pointed out previously, there are at least four published versions of the opd gene sequence, three of which were carried out by different laboratories using different techniques, yet presumably of the identical DNA sequence. Moreover, the sequence disclosed in the present patent application is yet another version of the same sequence derived with substantial research and development by the present inventors. While all of these sequences are substantially the same, the fact that there is not even to date a fully agreed upon sequence between those involved in the research in this field clearly points out the difficulty encountered by the inventors in obtaining a sequence for the gene they had isolated.

More importantly for the purposes of the present invention however, is the difficulty that was encountered in obtaining the translational open reading frame for the opd gene. Unlike genes isolated from the bacterium Escherichia coli, the genes isolated from soil bacteria like those of the present invention were not well-characterized at the time of the making of the present invention. Only a handful of Pseudomonas genes had been isolated at the time of the present invention and no Flavobacterium genes had been isolated to the inventors' knowledge.

Thus, while it was reasonable to presume that the initiation codon would be an ATG codon, it was just as reasonable to assume that the initiation codon was GTG (at least some art of which the

inventors were aware at the time of the making of the invention indicated GTG was a possible initiation codon in bacteria) and, in fact may have been an initiation codon altogether novel unlike the classical enteric bacteria. This increased the potential starting sites for the gene substantially especially in the GC-rich DNA of these soil bacteria. The fact that the initiation codon most likely included at least one, and possibly two, G nucleotide(s) further complicated the search for the proper coding sequence of the opd gene. This was particularly true since the inventors knew that they were likely to be at least partially incorrect as to the actual G's and C's in the sequence due to the phenomenon of GC compaction discussed above.

Further difficulty was quickly encountered when the inventors tried to sequence the minuscule amounts of partially purified organophosphorus acid anhydrase (OPA) obtained from E. coli cells transformed with the heterologous opd gene having failed to do so adequately in the host organisms. The very low activities associated with normal expression techniques as illustrated in the specification at p. 9 are indicative of the problems encountered by the inventors and others in obtaining enough purified protein to sequence for purposes of determining the actual coding sequence for the opd gene. Thus, as pointed out in the specification at p. 23, lines 10-34 and p. 25, lines 8-13, it became necessary for the inventors to use fusion proteins in order to overcome the substantial roadblocks they and others had encountered in purifying and sequencing the OPA enzyme. Moreover, in order to achieve the substantial purifications of the invention, effective amounts of expression of the membrane-associated enzyme had to be achieved in a heterologous cell such as E. Coli or in baculovirus-infected insect cells.

The Examiner's attention is additionally drawn to the fact that the Wild reference, which was a preliminary report in the earliest stages of the inventors' research, does not teach where the open reading frame occurs within the originally isolated fragment from the soil bacteria. In fact, the Wild reference teaches that it is

possible to enhance expression of the opd gene product by removing approximately 250 base pairs of DNA from the 5' flanking sequence of the fragment. To the contrary, the present invention teaches that removal of such a region of DNA from the opd gene-containing fragment eliminates any OPA activity (see, Fig. 2). Thus, if one were to follow the teachings of the Wild reference, one would place the initiation site of the opd gene at least 250 base pairs downstream of the PstI site and approximately at least 190 base pairs away from the actual initiation site. In fact, were one to make such a construction by deleting the first 250 base pairs from the PstI fragment, one would throw away the fragment containing the actual initiation site. What the disclosures of the Wild reference reiterates, in fact, is the confused state of the art prior to the present invention.

These type problems were recently the focus of concern for the CAFC. In Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200 (Fed. Cir. 1991), the defendants asserted error in the district court's legal conclusion that in this case the inventor's conception occurred simultaneously with reduction to practice. The defendants claim the inventor was the first to conceive a probing strategy of using two sets of fully-degenerate cDNA probes of two different regions of the EPO gene to screen a gDNA library. Defendants here further claimed that another inventor conceived this strategy in 1981, was diligent until he reduced it to practice in May of 1984 and thus should be held to be a § 102(g) prior art inventor over Amgen's inventor who reduced the invention to practice in September 1983.

The CAFC was presented, therefore, with the question of when exactly, in the cloning and sequencing of a previously unknown DNA sequence whose encoded amino acid sequence is also unknown, does reduction to practice occur. The Court held:

Prior to 1983, the amino acid sequence for EPO was uncertain, and in some positions the sequence envisioned was incorrect. Thus, until Fritsch (Chugai's inventor) had a complete mental conception of a purified and isolated

DNA sequence encoding EPO and a method for its preparation, in which the precise identity of the sequence is envisioned, or in terms of other characteristics sufficient to distinguish it from other genes, all he had was an objective to make an invention which he could not then adequately describe or define.

It is submitted by Applicants here that a similar situation existed in the invention of the present application. The amino acid sequence for OPA was entirely unknown prior to the disclosure by Applicants in a journal article less than one year prior to the filing of the present invention. Until that time, the location of the gene, the correct gene sequence, the start site and the putative amino acid sequence were not only purely speculative but actually incorrectly characterized. Thus, until the present inventors had "a complete mental conception of a purified and isolated DNA sequence" encoding the correct OPA amino acid sequence, "and a method for its preparation, in which the precise identity of the sequence is envisioned, or in terms of other characteristics sufficient to distinguish it from other genes," all the present inventors or any others had was "an objective to make an invention" which could not then be adequately described or defined.

Thus, while there are some similarities between the elements of the present invention and the Wild reference, the critical discoveries which allowed the inventors and others to successfully clone, sequence, and express high levels of opd gene product had to await the inventions described in the present application. For these reasons, the Applicants submit that the Wild reference is improperly cited by the Examiner as a barring reference under § 103. It is, therefore, requested that this basis of rejection be removed from the case.

- d. Mulbry et al. also does not teach the DNA sequence of the opd gene nor does it anticipate the difficulty that the present inventors encountered in obtaining the sequence and the initiation codon necessary for subsequent manipulation of the opd gene for purposes of the critical expression of the gene.

Mulbry et al. is a reference which represents a collaboration between the inventors and certain scientists at the U.S.D.A. to expand the U.S.D.A.'s results in cloning to the bacterium Flavobacterium. Again, as in the previously discussed reference of Wild et al., the Mulbry et al. reference does not teach the DNA sequence of the opd gene nor does it anticipate the difficulty that the present inventors encountered in obtaining the sequence and the initiation codon necessary for subsequent manipulation of the opd gene for purposes of the critical expression of the gene. Thus, the same arguments addressed above apply equally well to Mulbry et al.

Moreover, Mulbry et al. teaches away from the present invention in several critical ways. The Examiner's attention is drawn to the fact that not only does Mulbry fail to teach a DNA sequence for the opd gene, it fails to even teach one how to verify in Flavobacterium an active OPA enzyme. The only way that was used by Mulbry and co-workers to detect an opd gene in the Flavobacterium genome was by use of the probe provided to them by the present inventors. It will be understood by the Examiner and others of skill in the art that there absolutely is no requirement for any knowledge of the sequence of such a probe.

Mulbry teaches away from the present invention in yet another critical manner. The Mulbry reference teaches one of skill in the art to isolate a 7.3 kb EcoRI fragment from the Flavobacterium DNA or a 2.1 kb BamHI-EcoRI therefrom. Having so isolated such fragments, the Mulbry article at p. 928 column 2, lines 35-38 clearly states that no Flavobacterium clones possessed opd activity. Thus, were one of skill in the art to practice the Mulbry teachings, no heterologously expressed OPA enzyme would be obtained from the recombinant cells using the fragments obtained.

The fact that the Mulbry reference teaches the opd gene open reading frame to begin at a PstI site within the 2.1 kb BamHI-EcoRI fragment which itself is within the 7.3 kb EcoRI fragment is further evidence of a teaching away from the correct open reading frame of the present invention. Figure 3 of the Mulbry reference clearly

shows the open reading frame of the opd gene to begin at the PstI site and extend toward the EcoRI site downstream.

Thus, if one were to follow the teachings of the Mulbry reference, one would obtain large fragments of Flavobacterium DNA which, when placed in appropriate host cells would not provide an active protein for isolation and purification. There would be no way, therefore, to obtain a purified protein for subsequent purification and sequencing in order to determine the proper gene initiation site. According to the Mulbry reference, the initiation site of the gene occurred approximately at the PstI site which is more than 60 base pairs away from the actual site.

Thus again, while there are some similarities between the elements of the present invention and the Mulbry reference, the critical discoveries which allowed the inventors to successfully clone, sequence, and express high levels of opd gene product had to await the inventions described in the present application. Mulbry neither teaches nor suggests the combination of elements necessary to achieve the present invention -- in fact, it teaches away from the present invention. For these reasons, the Applicants submit that the Mulbry reference is also improperly cited by the Examiner as a barring reference under § 103. It is, therefore, requested that this basis of rejection be removed from the case.

- e. **The McDaniel (AZ) reference does not disclose the opd gene sequence and, moreover, teaches away from the present invention in a number of critical ways.**

The McDaniel reference (AZ) represents a Ph.D. dissertation of one of the inventors. It was preliminary in nature as to the studies which were ultimately to give rise to the inventions of the present application. Clear evidence of the preliminary nature of this reference is the fact that the DNA sequence of the opd gene is not disclosed herein although attempts to obtain such a sequence were clearly carried out as shown in the reference at the points recognized by the Examiner. The inventors were unable at the time of the publication of this reference to even provide preliminary

sequencing information since the difficulties heretofore described prevented them from accurate sequencing.

Moreover, even the limited sequencing that was carried out resulted in a serious error in estimating the initiation site of the opd gene. This is clearly indicated in Table 9 on page 100 of this reference. Here it can be seen that the opd gene is said to possess a GTG start site and various promoter sequences 5' thereof. In actuality, the bona fide start site is some 18 base pairs from the GTG identified in this reference and the 5' promoter regions are vastly different than those shown in the Table 9 of this reference (it is to be noted that the largest part of these differences are accounted for by the GC compaction problem noted before). Thus, if the skilled technician used the teachings of the McDaniel reference, he would clearly mistake the actual start site of the opd gene since it teaches away from the ATG site identified through substantial effort and inventive approaches to sequencing the DNA and protein as taught by the present patent application.

Furthermore, the McDaniel reference clearly points out the failure of the inventors at the time of the publication of this reference to determine the actual start site of the gene. The Examiner's attention is drawn to p. 98, lines 21-24 and p. 101, lines 1-2 of the McDaniel reference. It is made clear here that clarification of the start sites of the opd gene would require S1-nuclease mapping and/or purification and sequencing of the gene product. It was also made clear that these technologies were unavailable to the inventors as tools since purification of the membrane-bound enzyme and the isolation of mRNA had not been feasible. Had, of course, the DNA sequence on the start site and open reading frame been available to the inventors at the time of publishing this reference, it would most certainly have been included in its entirety and fully characterized. It was not since data were preliminary, flawed and internally inconsistent at the time.

The Examiner's attention is drawn to the important fact that there is no teaching in the McDaniel reference which definitively

shows a molecular weight of the OPA enzyme. Very clearly, molecular weight gels were inconclusive as to the weight of the protein (see Fig. 22). The approximately 1300 bp fragment isolated in this study potentially could code for a protein ranging from 10,000 to 65,000 Da ($[1300 \text{ bp} \div 3 \text{ bp/amino acid}] \times \sim 150 \text{ Da/amino acid} \approx 65,000 \text{ Da}$). There was no way to determine where, in this range, the OPA fell. The inventors at the time of the drafting of this reference postulated the existence of a 31,000 Da protein (as shown in Fig. 22 of the reference). However, this could not be confirmed since there were other prominent bands ranging from the 65,000 range and down (see e.g., band at approximately 26,000 Da) with similar characteristics and representing as likely a candidate protein.

Thus, while the McDaniel reference does give an indication of research in progress which led to the invention, it clearly does not teach one of skill in the art how to make the invention. In fact, the McDaniel reference teaches away from the current invention in important ways. For these reasons, Applicants submit that the McDaniel reference does not anticipate the present invention. Nor does this reference teach or suggest the combinations proposed by the Examiner and should, therefore, be removed as a basis for rejection of the claims.

- f. The Serdar et al. reference does not disclose a DNA sequence for the opd gene and, moreover, teaches away from the present invention in several critical ways.**

The Serdar reference is another preliminary reference which was indicative of the state of the art around the time of the McDaniel (AZ) reference discussed immediately above. The Examiner's attention is again drawn to the fact that no sequence information is provided in the Serdar reference. These authors did not publish sequence information on this gene until 1989. The Applicants submit that this is another indication of the difficulty encountered by the present inventors as well as others in obtaining the accurate sequence and the accurate start site for the gene which produces this membrane-associated enzyme in these soil bacteria.

Even more importantly, the Serdar reference clearly teaches away from the present invention. The Examiner correctly notes that the authors of the Serdar reference utilize both the PstI and BamHI restriction endonucleases in their studies. However, the Examiner's attention is drawn to the fact that only BamHI fragments of the opd-containing DNA were, in fact, isolated and cloned into the various expression vectors used in these studies. There was no attempt to size the fragment down to the PstI fragment taught by the present invention even though these authors were apparently aware of at least the 5' PstI site within the fragment.

The Serdar reference teaches away in another important respect, as well. In order to obtain increased expression, the authors of the Serdar reference teach one of skill in the art to move the cloned fragment back into the organism from which it was initially obtained (P. diminuta). This step clearly is not the way to provide access to a purified protein and is the opposite of the teaching of the present invention. High level expression of the OPA enzyme in the native strains in which it was first detected was well known in the art (see, e.g., McDaniel 1985 [AZ]). The problems, which problems were eventually overcome by the present invention, lay in the very fact that the native strains were not amenable to standard approaches in order to purify and sequence the protein.

It is submitted, therefore, that the Serdar reference does not make obvious the present invention. There is no teaching or suggestion in this reference to make the combinations which resulted in the present invention. It is requested that the Examiner remove the rejections under 35 U.S.C. § 103 as barring patentability of the application.

2. The Differences Between the Claims and the Cited Art

Claim 1 relates to an isolated and substantially purified bacterial organophosphorus acid anhydase gene comprising the DAN coding sequence shown in Figure 1.

No reference nor combination of references proposed by the Examiner teaches or suggests the requisite inventions of both a substantially purified and isolated bacterial organophosphorus acid anhydrase gene and the DNA sequence coding for the enzyme. Only with the teaching of the present disclosure is it possible to locate the start signal and open reading frame of the opd gene. Without these teachings, one is left with little more than has been known in the art for years. Without the sequence of the gene disclosed in the present invention, and in particular with the inability of the prior art to isolate and purify the OPA enzyme, no prior art references alone or in combination teach the skilled artisan the manner of locating, isolating or purifying the actual opd gene.

Claim 6 relates to a vector for producing OPA which vector has an integral opd gene with known start signal and defined sequence.

No reference nor combination of references teaches or suggests the requisite knowledge of the start site and the characterized sequence necessary to produce OPA from a recombinant vector as claimed in claim 6. Only by following the teachings of the present invention could one of skill in the art have predictably and with relative certainty obtained such requisite information. The Examiner's attention is again drawn to the limitations that existed at the time of the making of the present invention.

- (1) Few sequences existed for genes from soil bacteria, in particular, no sequences were known for Pseudomonas diminuta or Flavobacterium bacterial genes;
- (2) Thus, there was no way to predict for certain the nature of the start site, promoter, internal sequences, terminators and the like for these soil bacteria;
- (3) The DNA of these bacteria was known to have a high GC content and, thus, the sequencing was commensurately difficult;
- (4) The difficulty in sequencing (GC compaction) caused the inventors numerous difficulties since the likelihood that

G's and C's were either missing or wrongly placed substantially increased the likelihood of incorrect placement of start signals containing G's ("ATG" or "GTG" were the signals known at the time of the making of the invention);

- (5) Certain of the prior art references clearly taught away from the present invention; and
- (6) The prior art references must lead one of skill in the art to make the combinations of art, which none of the references do; and,
- (7) Even if the prior art references are properly combinable, they do not teach the necessary elements of the start site and the gene sequence.

Claims 12 and 14 relate to the expression of opd in microorganisms or eukaryotic cell lines. There is simply no teaching or suggestion in the art that indicates heterologous expression would be possible at levels necessary to achieve the successful purification of the membrane-associated protein OPA.

The Examiner's attention is additionally drawn to the failure of any prior art reference to teach or suggest the combination of the opd gene with a heterologous promoter for heterologous expression in a host other than the original host. This failure in the prior art is a direct result of the lack of knowledge about the start site and sequence provided by the present invention. Even where the opd gene is expressed under the control of its own promoter, the increased expression is achieved in a soil bacterium and occurs by control of the copy number of the vector.

Moreover, there is nothing in the art that suggests that a membrane-associated protein from soil bacteria could be expressed as an active protein in an eukaryotic cell line.

Therefore, it is respectfully submitted that no reference alone or in combination teach the critical aspects of the present invention. Even if the references are properly combinable as

proposed by the Examiner, the combinations do not derive the teachings disclosed in the present invention.

3. Level of ordinary Skill in the Art

The Graham inquiries point to a conclusion of nonobviousness of the present claims regardless of the presumed level of ordinary skill in the art. However, absent evidence to the contrary, a person of ordinary skill in the art is presumed to be one who essentially follows conventional wisdom and does not undertake to innovate. As stated by the Federal Circuit in Standard Oil Co. v. American Cyanamid Co., 227 U.S.P.Q. 293, 298 (Fed. Cir. 1985):

A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which.
(emphasis supplied)

Applicant submits that one who follows conventional wisdom would not extrapolate the subject matter of the present claims from the teachings of the references proposed by the Examiner. Accordingly, it is submitted that none of the references are combinable in the manner supposed by the Examiner. More importantly, there is clearly no motivation in any of these references relied upon by the examiner to make the combinations proposed by the Examiner. Specifically, none of the cited references suggest. The requisite start signal and gene sequence disclosed only in the present application. As the Patent and Trademark Office Board of Appeals stated in the case of Ex Parte Chicago Rawhide Manufacturing Co., 223 U.S.P.Q. 351, 353 (PTO Bd. App. 1984);

The prior art must provide a motivation or reason for the worker in art, without the benefit of the Appellant's application, to make the necessary changes in the referenced device.
(emphasis added)

In the present case, no motivation is provided by any of the references to produce the present invention. Only by hindsight and with the knowledge of the present application could one reasonably

propose that the cited prior art renders the invention obvious. Furthermore, as pointed out on numerous occasions by the Federal Circuit, the use of "hindsight" gleaned from the Applicants' specification is an entirely improper means for finding a motivation to combine cited references. In re Corkill, 226 U.S.P.Q. 1005, 1008 (CAFC 1985).

Even if the references are properly combinable, they nevertheless fail to teach or suggest the invention. As pointed out above, none of the references discloses the requisite combination of known start site and gene sequence. For the foregoing reasons, it is respectfully submitted that the invention as defined by claims currently in the case are patentable over the art.

4. Secondary Considerations

As the Court of Appeals for the Federal Circuit has unequivocally stated in *Custom Accessories Inc. v. Jeffrey-Allan Industries Inc.*, 1 U.S.P.Q.2d 1196 (Fed. Cir. 1986):

Objective evidence of non-obviousness includes commercial success, long-felt but unresolved need, failure of others, and copying. When present, such objective evidence must be considered. It can be the most probative evidence of non-obviousness in the record, and enables the district court to avert the trap of hindsight. On the other hand, the absence of objective evidence does not preclude a holding of non-obviousness because such evidence is not a requirement for patentability.

These objective criteria are individually addressed below as they each apply to the present invention. The Examiner is respectfully requested to give all such evidence the requisite consideration.

Long-felt But Unresolved Need

The continuing long-felt and unresolved need in our communities for safe and effective means to eliminate and protect against the toxic effects of organophosphorus compounds is well known and has continued to be an issue at the forefront of public attention. This continuing and unresolved concern was poignantly and graphically

d monstrated in at least two recent tel vision broadcasts which are provid d for the Examiner's r view.

The sensitivity of certain individuals to home pest control application of organophosphorus pesticides such as dursban was the topic of a thirteen (13) minute segment of NBC Today on May 16, 1991 (Exhibit B). In this documentary (pp. 26-28) Katherine Couric, co-host, narrates the story of Mrs. Chris Weidner, an individual who suffers from a sensitivity to organophosphorus pesticides such as dursban. The graphic account related in this exhibit speaks for itself.

However, the Examiner's attention is particularly drawn to the discussion between Dr. Marion Moses of The Pesticide Education Center and Warren Stickle of the Chemical Producer's and Distributor's Association. Dr. Moses' comments are apparently much more in keeping with current EPA evaluations of these toxic compounds than are Mr. Stickle's. See, e.g., Exhibits C-H which is a collection of "Pesticide Fact Sheets" published by the EPA, which fact sheets clearly show the concern which the government has concerning compounds such as ethyl parathion, Diazinon, fenitrothion, coumaphos, acephate and malathion.

Even more alarming was the report (Exhibit I) presented by Peter Jennings on ABC World News Tonight concerning Diazinon poisonings due to home applications, especially such exposures to small children, shown on May 9, 1991. In this documentary, reporter Bill Greenwood narrates the tragic Diazinon poisoning of Mr. Tom Latimer. Again, the Examiner's attention is drawn to the tragic consequences of such pesticide poisonings. The Examiner is provided a transcript at this program which is not as descriptive as the video tape itself. If so desired, the Applicants can produce the tape for viewing at the Examiner's convenience.

Protection systems for home applications of organophosphorus pesticides are certainly of paramount need and, as yet, remain an unresolved problem for modern science. The Examiner's attention is additionally directed to the desire by major producers of these pesticides to develop technology to degrade pesticides both at the

production level and at the consumer level. The Examiner's attention is drawn to the March 4, 1991 CONFIDENTIAL letter to Ms. Ann Levy (whose company TECHSOURCE represents Applicants in licensing the present invention) from American Cyanamid Co. (Exhibit J) and to the CONFIDENTIAL letter of June 5, 1991 to Dr. D. R. Eger (of the same firm) from the Ortho Division of the Chevron Chemical Co. (Exhibit K). These letters both further support the long and unsatisfied need in the commercial community for the products and processes of the present invention.

However, detoxification problems of startling proportions involving organophosphorus neurotoxins confront both government and commercial endeavors as well and are not limited to home pesticide use. The Examiner is reminded of the surprising finding by the present inventors that the enzyme of the present invention was effective in detoxifying one of the most common nerve agents produced by the military. The Examiner's attention is first drawn to a recent newspaper report by Keith Schneider of the New York Times published in the Houston Chronicle on Sunday, May 5, 1991 (Exhibit L, p. 12A). It will be noted in that article, that:

Hampered by flaws in design and operation, the Army's program to incinerate the nation's enormous stockpile of chemical weapons is falling years behind schedule, experiencing huge cost increases and stirring public protests in six states and the South Pacific. ... The project is part of the more than \$200 billion the Pentagon has proposed to spend in the next 30 to 50 years to prevent the spread of poisons and clean up its contaminated bases and munitions factories. ... [T]he Army has proposed burning all its mustard gas and nerve agents [primarily organophosphorus compounds] -- 60 million to 70 million pounds of the world's deadliest chemicals -- in nine incinerators.

As noted in the specification, p. 2, lines 1-5, the U.S. Army Research office provided funding for portions of the research involved in the making of this invention. More recently, the Department of the Navy has provided similar funding. While incineration has apparently been chosen as the most expeditious means of detoxifying these compounds, the Army maintains interest in using the enzyme, if they are produced on a commercially feasible

scale, to handle localized detoxification in spills, cleanups and transfer operations.

Commercial Success

Coupled with the clearly existing long-felt and unresolved needs established above is the initial proof of commercial success for the pilot-scale products and processes of the present invention. As evidence of this initial success, the Examiner's attention is drawn to the letter discussing a contractual agreement between the Chevron Chemical Company and the Assignee of the present invention (Exhibit M). Again, the confidentiality of the this Agreement is expressly pointed out to the Examiner and he is requested to so maintain the Agreement and its contents in strictest confidence.

This Agreement notes that payment of \$25,000 for evaluation of the products and process of the present invention is anticipated. That this commercial success has been a result of the nature and acceptance of the invention rather than from some relatively unrelated fact, such as marketing is most clearly indicated by the sophistication of the purchasing party, the Ortho Division of the Chevron Chemical Company. Since the market for this product is as yet undeveloped, no data can be presented as to market share, growth in market share, replacement of earlier products sold by others, or retail dollar amounts. However, the nexus required to exist between the claimed invention and the commercial success is evident.

Another indicia of the commercial success of the present invention is the apparent interest in supporting research and development of the recombinant enzyme by biotechnology companies such as Amgen. Cüneyt M. Serdar, the first author of Serdar et al. (1989), began research in this area under Douglas M. Munnecke at the University of Oklahoma (see, e.g., Serdar et al. [1982]), completed a Ph.D. in this area at the University of Texas at Austin under David T. Gibson (see, e.g., Serdar and Gibson [1985]) and apparently was encouraged to continue the work after he was hired by Amgen Inc. of Thousand Oaks, CA (see, e.g., Serdar et al. [1989]). This work was apparently carried out by Serdar at Amgen even in the face of

all of the prior art cited by the Examiner in this Office Action and other prior art made of record in the Information Disclosure Statement filed in this case. Since it is very unlikely that a commercially successful biotechnology firm such as Amgen would fund research and development of a project that held no commercial potential for success, one may infer that at least Amgen considers the development of the recombinant OPA enzyme to have a potential for commercial success.

Copying

Copying the claimed invention, rather than one in the public domain, is indicative of non-obviousness. *Specialty Composites v. Cabot Corp.*, 6 U.S.P.Q.2d 1601 (Fed. Cir. 1988).

The Examiner's attention is drawn to the clear copying by others of the present invention. If the skilled artisan were to follow the teachings of the prior art, he would fail to derive the present invention. For instance, if the skilled artisan were to follow the teachings of either Serdar, et al. or of Mulbry et al., he would isolate a very large segment of DNA from the native plasmid (in excess of 5 kb). He would then attempt to express this heterologously and fail (see, e.g., both references). He would, therefore, be unable to obtain purified OPA. Lacking the purified protein, he would have no way to determine the location of the opd gene. It is only by copying the methods of the present invention that others were able to produce the sized-down DNA fragment. In particular, if the skilled artisan were to combine the teachings of McDaniel et al. which incorrectly showed the position and nature of the start signal, he would fail. Only by copying the start signal and sequence disclosed by the present invention were others capable of repeating the invention.

Failure of Others

The differences between the prior art and the invention defined by the asserted claims, the availability of that art to all workers in the field, the failure of established competitors in a highly competitive market to make the invention despite the incentive to do so, the admittedly non-obvious performance benefits realized through the claimed invention, the impressive commercial success of the claimed product, the praise of independent commentators and the forbearance of competitors from infringing the patent all go to confirm the claimed invention was not obvious at the time it was made to a person of ordinary skill in the art. *S.C. Johnson & Son, Inc. v. Carter-Wallace, Inc.*, 225 U.S.P.Q. 1022 (N.Y. 1985).

Moreover, even the prior art cited by the Examiner shows the failures to achieve the present invention by others. The Examiner's attention has been drawn in arguments made above to numerous of these failures. However, in summary, it can be unequivocally stated that no other worker in the field, including the inventors themselves, had achieved the present invention until it was achieved by the inventors and disclosed in the present application. In fact, others had failed to:

- (1) identify the actual start signal;
- (2) sequence the gene;
- (3) heterologously express sufficient quantities of OPA to allow determination of the amino acid sequence; or
- (4) transform eukaryotic cell lines with opd.

These failures occurred even in the face of readily available prior art to all workers in the field, and even in view of the impetus for established competitors in the highly competitive market to make the invention.

From the foregoing remarks, it is submitted that a conclusion of nonobviousness is compelled. The Applicant has addressed each of the Examiner's comments in the Office Action as they pertain to Section 103 rejections.

VI. Conclusion

This response to the Office Action of May 24, 1991 has addressed the rejections based upon Sections 112, 102(b) and 103 as pointed out by the Examiner. Accordingly, the response is believed to be a complete response to the Office Action and, therefore, that reconsideration is appropriate. Claims 1-16, 30-33, 37-40 and 71 appear to be in condition for allowance and such favorable action is respectfully requested.

Respectfully submitted,

Date: October ²⁴~~23~~, 1991

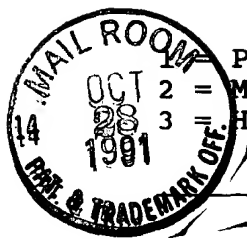
C. Steven McDaniel
C. Steven McDaniel

Reg. No. 33,962
ARNOLD, WHITE & DURKEE
P. O. Box 4433
Houston, Texas 77210
(512) 320-7200

by Terry D.
Morgan
Reg. No. 31,181

H:\TAMK\112\PTO\01.MCS

COMPARISON OF opd SEQUENCE DISCLOSED
IN PATENT APPLICATION SERIAL NO. 07/344,258
TO PUBLISHED SEQUENCES



Patent Application
2 = McDaniel et al. (1988)
3 = Harper et al. (1988)

4 = Serdar et al. (1989)
5 = Mulby & Karns (1989)
6 = Corrected Sequence

1 C T G C A G - - - C C T G A C T C G G C A C C A G T C G C T 30
2 - - -
3 - - -
4 G T C
5 - - -
6 - - -

1 G C A A G C A G A G T C G T A A G C A A T C G C A A G G G G 60
2
3
4
5
6

opd coding Sequence

1 G C A G C A T G¹ C A A A C G A G A A G G G T T G T G C T C A 90
2
3
4
5
6

¹ consensus start codon

[]= a blank space means identity (homology) with the sequence in the patent application

[-]= a hyphen means a base is missing in the sequence in which hyphen occurs but which base occurs in another sequence

```

1  A G T C T G C G G C C G C - A - G - G A A C T C T G C T C G 120
2                                - G - A -
3                                - G - A -
4                                C G C A G
5                                C G C A G
6                                C G C A G

```

```

1  G C G G C C T G G C T G G G T G C G C G A - C G T G G C T G 150
2                                -
3                                -
4                                G
5                                G
6                                G

```

```

1  G A T C G A T C G G C A C A G G C G A T C G G A T C A A T A 180
2                                G C
3                                G C
4
5
6

```

```

1  C - G T G C G C G - T C C T A T C A C A A T C T C T G A A G 210
2  2 - -
3  - -
4  C G
5  C G
6  C G

```

```

1  C G G G T T T C A C A C T G A C T C A C G A G G A C A T C T 240
2
3
4                                C
5                                C
6                                G/C

```

² Mulby and Karns (1989) cite in their Fig. 5 that Harper et al. (1989) has a "T" at this position. That is incorrect. Harper et al. show a "C" at this position.

[]= a blank space means identity (homology) with the sequence in the patent application

[-]= a hyphen means a base is missing in the sequence in which hyphen occurs but which base occurs in another sequence

1 G C G G C A G C T C G G C A G G A T T C T T G C G T G C T T 270
 2 C G -
 3 C G -
 4
 5
 6

1 G G C C A G A G T T C T T C G G T A G C C G C A A A G C T C 300
 2 -
 3 -
 4
 5
 6 ?/C

1 T A G C G G A A A A G G C T G T G A G A C G A T T G C G C - 330
 2 -
 3 C -
 4 G C
 5 G C
 6 G C

1 G C - - C A G A G C G G C T G G C G - G C G T G C G A A C G 360
 2 T
 3 T - - - -
 4 G C T - - - -
 5 G C T - - - -
 6 G C T - - - -

1 A T T G T C G A T G T G T C G A C T T T C G A T A T C G G T 390
 2
 3
 4
 5
 6

1 C G C G A C G T C A G T T T A T T G G C C G A G G T T T C G 420
 2
 3
 4
 5
 6

[]= a blank space means identity (homology) with the sequence in the patent application

[-]= a hyphen means a base is missing in the sequence in which hyphen occurs but which base occurs in another sequence

1 C G G G C T G C C G A C G T T C A T A T C G T G G C G G C G 450
 2 -
 3 -
 4
 5
 6

1 A C C G G C T T G T G G T T C G A C C C G C C A C T T T C G 480
 2
 3
 4
 5
 6

1 A T G C G A T T G A G G T A T G T A G A G G A A C T C A C A 510
 2
 3
 4 A G
 5 A G
 6

1 C - A G T T C T T C C T G C G - T G A G A T T C A A T A T G 540
 2 T G
 3 T G
 4
 5
 6

1 G C A T C G A A G - A C A C C G G A A T T A G G G C G G G C 570
 2 T
 3 T
 4
 5
 6

1 A T T A T C A A G G T C G C G A C C A C A G G C A A G G C G 600
 2
 3
 4
 5
 6

[]= a blank space means identity (homology) with the sequence in the patent application

[-]= a hyphen means a base is missing in the sequence in which hyphen occurs but which base occurs in another sequence

1 A C C C C C T T T C A G G A G T T A G T G T T A A A G G C G 630
 2
 3
 4
 5
 6

1 G C C G C C C G G G C C A G C T T G G C C A C C G G T G T T 660
 2
 3
 4
 5
 6

1 C C G G T A A C C A C T C A C A C G G C A G C A A G T C A G 690
 2
 3
 4
 5
 6

1 C G C G A T G G T G A G C G A G G C A G G C C G C C A T T T 720
 2
 3
 4 - -
 5 - -
 6 - -

1 T T G A G T C C G A A G - C T T G A G C C G - T C A C G G G 750
 2 - -
 3 - -
 4 G C
 5 G C³
 6 G C

³ Incorrectly left out of Mulbry and Karns as a difference in Fig. 5.

[]= a blank space means identity (homology) with the sequence in the patent application

[-]= a hyphen means a base is missing in the sequence in which hyphen occurs but which base occurs in another sequence

1 T T T G T A T T G G T C A C A G C G A T G A T A C T G A C G 780
 2
 3
 4
 5
 6

1 A T T T G A G C T A T C T C A C C G C C C T - G C T G - - C 810
 2 - -
 3 - -
 4 C C G
 5 C C G
 6 C C G

1 G C G G A T A C C T C A T C G G T C T A G A C C A C A T C C 840
 2
 3
 4
 5
 6

1 C G C A C A G T G C G A T T G G T C T A G A A G A T A A T G 870
 2
 3
 4
 5
 6

1 C G A G T G C A T C A C C G C T C C T G G G C A T C C G T T 900
 2
 3
 4 G C
 5 G C
 6 G C

1 C G T G G C A A A C A C G G G C T C T C T T G A T C A A G G 930
 2
 3
 4
 5
 6

[]= a blank space means identity (homology) with the sequence in the patent application

[-]= a hyphen means a base is missing in the sequence in which hyphen occurs but which base occurs in another sequence

1 C G C T C A T C G A C C A A G G C T A C A T G A A A C A A A 960
 2
 3
 4
 5
 6

1 T C C T C G T T T C G A A T G A C T G G C T G T T C G G G T 990
 2
 3
 4
 5
 6

1 T T T C G A G C T A T G T C A C C A A C A T C A T G G A C G 1020
 2
 3
 4
 5
 6

1 T G A T G G A T C G C G T G A A C C C C G A C G G G A T G G 1050
 2
 3
 4
 5
 6

1 C C T T C A T T C C A C T G A⁴ G A G T G A T C C C A T T C - 1080
 2 -
 3 -
 4
 5 C
 6 C

⁴ Stop codon postulated by patent application.

[]= a blank space means identity (homology) with the sequence in the patent application

[-]= a hyphen means a base is missing in the sequence in which hyphen occurs but which base occurs in another sequence

```

1 T A C G A G A G A A G G G C G T C C C A C A G G A A A C G C 1110
2
3
4
5
6

```

```

1 T G C C A G G C A T C A C T G T G A C T A A C C C G G C G C 1140
2      G
3      G
4      G
5      G
6      G

```

```

1 G G T T C T G T G T C A C C G A C - T T G C - - - C G T G C 1170
2      - - -
3      - - -
4      - C G G G -
5      - C G G G -
6      - C G ? ? ?

```

```

1 A T G6 A C G C C A T C T G G A T C C T T C C A C G C A G C G 1200
2
3
4      G C
5      G C
6      ? ?

```

```

1 G C C A C T A T T C C C C G T C A A G A T A C C G A A C G A 1230
2
3
4 C G
5
6 ? ?

```

⁵ Inventors have not re-sequenced the DNA 3' of this point since it most likely is not included within the open reading frame.

⁶ Stop codon postulated by Mulbry and Karns/Serdar et al.

[]= a blank space means identity (homology) with the sequence in the patent application

[-]= a hyphen means a base is missing in the sequence in which hyphen occurs but which base occurs in another sequence

1 T G A A G T C G C G C A T C G A T C G A T A G G C A T C T T 1260
 2 - - - -
 3
 4
 5
 6 ? ? ? ?

1 C A A T G T G A T C A G G G C T G C C A C C T C C A A A G C 1290
 2
 3
 4
 5 T⁷
 6 ? ?

1 C G G T G G C C A C C C C T G T C G A T A G T C T T G A G G 1320
 2
 3
 4 -
 5 -
 6

1 G A C G G T A G C G A C G A C C G T G C T T T T C G T G A A 1350
 2
 3
 4 - - G C A C - -
 5 - - G C A C - -
 6

1 C T G C A G 1356
 2
 3
 4
 5
 6

h:\amk\112\pto\02.mcs

⁷ Mulbry and Karns incorrectly show Harper et al. places a "C" here.

[]= a blank space means identity (homology) with the sequence in the patent application

[-]= a hyphen means a base is missing in the sequence in which hyphen occurs but which base occurs in another sequence

**NBC
Today
May 16, 1991
7:00-9:00 AM EDT**

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Bryant Gumbel, co-host:

Good morning. Secretary of State James Baker has completed his talks in the Mideast. After a fourth meeting with Israeli Prime Minister Yitzhak Shamir, it appears that Baker's attempts to convene a regional peace conference have failed. Israeli and Syrian conflicts over procedural questions and the role of the UN would play in any talks remain unresolved. Though Baker left Israel talking of progress and further efforts, he's heading home empty-handed today, Thursday, May the 16th, 1991.

Gumbel: Good morning. And welcome to Today on a Thursday morning. Katie's just moving them in and out of here. I come back in and Joe is gone. Where did he go?

Katherine Couric, co-host:

We sent him up to do some organic lawn--I--not lawning, I guess gardening. Not gardening, though, really. He's taking--what's wrong with you, Al?

Gumbel: He's going to be helping out in the After Eight. We're going to talk about lawns and pesticides.

Couric: Thank you, Bryant.

Gumbel: Right. I figured as much. Anyway, Gene Shalit's going to be along, he's in the Critic's Corner. We've got some ice cream on tap, our Gadget Guru is here. We've some other surprises as well on a busy Thursday morning. Let's get the morning started at the news desk. As always, Faith Daniels.

Faith, good morning.

Faith Daniels, anchor:

Good morning, Bryant and Katie. Welcome back.

Gumbel: Thank you.

Daniels: Good morning, everyone.

Faith Daniels, anchor:

On his fourth try at a formula for peace in the Middle East, Secretary of State Baker appears to have come up empty-handed. Once again, Baker is coming home, leaving Israel and its Arab neighbors at odds about virtually everything. Martin Fletcher is with us now from Tel Aviv.

Good morning, Martin.

Martin Fletcher reporting:

Good morning, Faith. Baker has his work cut out putting a positive spin on this peace mission. It ends with no deal of any kind. But both Israel and Syria have appealed to Baker to keep trying.

Four meetings in 24 hours gave rise to some optimism, but in the end the same two problems dashed hopes of a surprise breakthrough.



James Baker: There remains to be resolved the--the question of the role, if any, of the United Nations in--in the process, and the question of the--the extent to which any conference might reconvene with the consent of all the parties. Those are the only--those are the only two areas, that I'm aware of, of continuing disagreement.

Fletcher: The areas that really divide Israel and Syria, though, literally and politically, are the Golan Heights. Israel wants to keep them, Syria wants them back. And, for all of Baker's efforts to narrow down the differences, he says there's more agreement than disagreement. In the end there won't be peace between Israel and Syria until both sides really want it.

Baker's next step is to report to President Bush in Washington, and decide whether and how to continue his peace mission. The betting here is the peace mission will continue, but not through such high profile shuttle diplomacy. Faith:

Daniels: Martin, if not shuttle diplomacy, then what?

Fletcher: Well, the only real way forward, you know, now could only be through what everybody has asked for on--on the left wing in Israel and the right wing here has feared, and that's pressure, pressure by America on Israel and also pressure by Russia on Syria, because until Israel and Syrian both really want peace, well there just won't be peace. Faith:

Daniels: All right. Thank you, Martin Fletcher.

Faith Daniels, anchor:

Sheriff's deputies stormed a Los Angeles city bus early today, and put an end to a three-hour standoff. Deputies shot and killed a woman who had opened fire aboard the bus as it passed through Beverly Hills. The woman killed one passenger. About 20 others fled from the bus when the first shots were fired.

Faith Daniels, anchor:

There's a heated dispute over AIDS in the Pacific northwest involving medical personnel who are also patients. The story from KING-TV's Brendan McLaughlin.

Brendan McLaughlin reporting:

A controversial policy at the University of Washington would bar doctors with AIDS from the operating room. It has focused a national debate on AIDS in the medical profession.

Eric Larson (University Of Washington Medical Center): If you are doing a procedure, an invasive procedure that might result in the spread of the virus to a patient and you're infected, you shouldn't be doing it.

McLaughlin: And, under this provision, can't be doing it?

Larson: Right.

McLaughlin: An invasive procedure is one where bodily fluids can get into the eye or an open wound. Surgeons are already trained to regard all blood as a toxic substance, but even so, the chances of transmitting the AIDS virus can be as low as one in a million.

Nancy Campbell (Northwest AIDS Foundation): The concern is where does this stop?

McLaughlin: Aids advocacy groups are suspicious of what they see as another attempt to limit the rights of the HIV-positive.

Campbell: Why don't we look at the risk that you run from having a doctor who's impaired on some level? Perhaps has an alcohol problem or a drug problem. There's a whole list of areas that we've never looked at. Why do we singularly now look at HIV?

McLaughlin: Under the policy, medical students would be forced out of programs that involve surgery.

Larson: It would not make sense to train somebody to do something that eventually they would not be allowed to do by the policy we have.

McLaughlin: University health officials believe the policy is fair and legal because AIDS testing under the rules would be voluntary. Brendan McLaughlin for NBC News, Seattle.

Faith Daniels, anchor:

President Bush wants to give China another year of most favored nation trade status. But he may have to make a deal with Congress. Capitol Hill critics point to China's human rights problems and its selling of weapons in the Middle East. The White House indicates it might put conditions on a new trade agreement tying it to reforms on politics and trade.

Faith Daniels, anchor:

On the foreign financial markets today, stock prices lost ground in Tokyo for the fifth day in a row. In London, trading opened with a small gain.

Faith Daniels, anchor:

The common market countries are flexing their economic muscles in the name of public health. They're considering a ban on cigarette advertising covering all 12 member nations. More from Today foreign editor, Dennis Murphy.

Dennis Murphy reporting:

The Marlboro Man may be about to lose his Formula One car. Billboards advertising cigarettes would be plastered over. By 1993, if the European Commission has its way, smokers will only know about competitive brands by word of mouth. Or maybe smoke signals.

Unidentified Woman #1: I remember being very influenced by, for instance, Benson and Hedges advertising when it was in the cinema. They were fantastic adverts. They were beautiful. It's just a pity they were for smoking.

Unidentified Man #1: If you're influencing people to smoke, you're basically influencing them to kill themselves.

Murphy: DC officials estimate 440,000 Europeans die every year as a result of smoking.

David Pollock (Smoking Opponent): We will commit wholeheartedly, as does the whole of the health community in Great Britain. And it really puts the government on the spot to show whose side they are on.

Murphy: British and German commissioners voted against the EC proposal, and it is by no means certain the ban will pass all the legislative obstacles and become European law. Europe's cigarette manufacturers cut through the smoke and fire with a statement that the advertising ban is, quote, 'At odds with market realities.' Dennis Murphy, NBC News, London.

Faith Daniels, anchor:

And in sports, in Stanley Cup action, Minnesota beat Pittsburgh 5-4 to take a one game to none lead. Game two is tomorrow night.

It's 7:07.

Bryant Gumbel, co-host:

All right. Faith, thanks so very much.

Time to--you didn't give the basketball scores, either. Pistons beat the Celtics, also.

Daniels: Well, Pitts...

Gumbel: Three-two lead in that series.

Daniels: ...Pittsburgh's not in it.

Gumbel: Oh, I see.

Willard Scott been away for, what, a couple of days?

Al Roker reporting:

Couple of days.

Gumbel: Sorry. I've been--I've been sleeping in.

Roker: You've been away.

Katherine Couric, co-host:

You've been out of it.

Gumbel: Well, you even asked yesterday, and June called.

Couric: Right.

Gumbel: Said I was...

Couric: Right. You were sleeping, in fact.

Gumbel: Yeah, I was--was sleeping.

Roker: She woke you up to tell you that we were talking about you.

Gumbel: No, missed that part of it.

How are you, my friend?

Couric: Al says that I didn't come up with-- that I didn't--I can't talk today. That I haven't invented a new word, that there's no such word as lawning.

Gumbel: Oh, is lawning...

Couric: It's lawn care.

Roker: Well, it's a new sport. It's a sport.

Gumbel: Lawning?

Roker: They--they play it in Iceland.

Gumbel: Can you not use the--can you not--verb--put it in verb form?

Couric: I don't think so, Bryant.

Roker: We're going to go lawning. Hee-hey, let's go! Ooop, three points for crabgrass! Ho-ho!

Let's take a look right now what's going on out there today. (Weather follows.)

That's the latest at 7:09. Now here's Bryant.

Gumbel: All right, Al, thanks very much.

Bryant Gumbel, co-host:

On Close Up this morning, education. Later this morning in Washington entrepreneur Chris Whittle plans to detail an idea that has some educators nervous. The man who put commercials in the classroom with his Channel One news service will announce plans for 200 private for-profit schools across the country that he says will change the way American children learn. He's at our NBC News bureau in Washington this morning to explain that to us.

Chris Whittle, good morning.

Chris Whittle (Whittle Communications): Good morning, Bryant.

Gumbel: No one disputes the idea of the need for a better mousetrap, but, in educational sense, how are your schools going to be different?

Whittle: I think if you went to one of these schools in four years when we plan to open them that you wouldn't recognize them, compared to a typical American school today. And they'll be as different as a light bulb is to a candle. Anywhere from how they're organized to the way subjects are taught to how the school is managed, we plan to literally take apart the old school and put it back together using both old and new parts.

Gumbel: Your--your plans right now, and correct me if I'm wrong, call for an outlay of somewhere between two-and-\$3 billion. Is it your plan to get outside corporate funding for that?

Whittle: Our plan is is that we will have to raise capital from a variety of large companies around the United States, yes.

Gumbel: And what do you promise corporations in return for their investment?

Whittle: Basically, they have become investors in the business and they would receive dividends, just like you do at any particular company.

Gumbel: Do they become advertisers to the school children beyond the regular Channel One news service that you envision?

Whittle: Not at all, meaning we--we are not planning to fund this through advertising.

Gumbel: So, we--we wouldn't see McDonald's signs down the halls and advertisements?

Whittle: That's not the plan. No.

Gumbel: No Exxon ads in the--in the textbooks, things like that, that the educators are worried about?

Whittle: Right.

Gumbel: Let me ask you a little bit about this. I mean, if--if these are run for profit, would that be the primary motive, and wouldn't education suffer if that were true?

Whittle: The primary motive is not profit. The primary motive here is to bring a new model school to the United States. And--and we think that private industry is in a position, because it doesn't have to operate with all of the--the terrible restrictions that most schools in this country are burdened with, to really start over in a way that we need to in this country. We think a lot of public educators are--are trying very hard to do that, but they are burdened by laws and regulations, and a private company really is free to act boldly, and we think we need that in education.

Gumbel: Yeah. You're--you're talking of--of--if new American schools, that's the same terminology that I'm sure you know the president has used as he talks about the--the new 500-plus schools that he would like the federal government to fund. In any way, do you see yours being in competition with his?

Whittle: I think the essence of the Bush plan, which we are big supporters of, is that they want competition in education. And they want many different people striving for different solutions to this problem. And so, we--we're a big supporter of it, and in some ways we'll be in competition, but we think that's good.

Gumbel: May I assume that you have already talked this through this with your fellow Tennessean, Lamar Alexander, who is now secretary of education, and who sat on your board at Whittle Communications?

Whittle: We did brief the Department of Education, as we did 15 other education groups here in Washington in the last three days, but not Mr. Alexander.

Gumbel: Not Mr. Alexander? You don't know his sentiments about this one way or the other at this point?

Whittle: I don't, no.

Gumbel: You--you're planning a tuition, what, somewhere in the four-to-\$5,000 range?

Whittle: Our plan is, is we've got to make a school work for the same amount of money that the public education system makes a school work. And the reason is, one of our key objectives here is to provide a model that public schools can copy if they choose. And if we come up with an expensive, elitist model, there's no way that a public school can follow that example.

Gumbel: So who will get to attend these schools?

Whittle: That's another interesting difference between us and most private schools. We will have no entrance requirements for students. We will randomly select them just as public schools have to accept all comers. Some will say, 'Well, yes, but they have to pay,' and we recognize that, and that's why 20 percent of the students in our schools are going to be on full scholarship. And we have to build that into our cost plan.

Gumbel: I ask this as a final note, Mr. Whittle, and please don't assume anything by it, I mean we--we assume you are a very good American who's interested in education, as we all are, but you are, first and foremost, a businessman. What's in this for Chris Whittle?

Whittle: The most important thing that's in this for Chris Whittle is I think this is a wonderful thing for me to do with the next 20 years of my life. And I think it will change it, I think, in many ways. I've been trained to do it. And I feel lucky that the opportunity to do it is there.

Gumbel: We will keep an eye open. Chris Whittle, thank you.

Whittle: Thanks.

Gumbel: Take care. Good luck.

Whittle: 'Bye.

Gumbel: Seven-fourteen. We're back in a moment. This is Today on NBC.

Katherine Couric, co-host:

The nation's crack epidemic is six years old. And among those paying the heaviest price are the children of crack-addicted mothers. But a new Senate Judiciary report out today shows that school systems across the country are starting to pay the price, too. NBC's Lisa Myers reports.

Lisa Myers reporting:

The report finds that special education programs around the country are being flooded with three to five year olds in need of help. The increases are largest where the crack epidemic has been worst. In New York City, the number of pre-schoolers enrolled in special education jumped 25 percent this year.

Theodora De Soyza (Learning Center Director): Five years ago we had two children. Today we have 19 children whose parents were, that we know of, were on drugs.

Myers: In Los Angeles, pre-school special ed enrollments have doubled since 1986, partly because of crack. That has further strained school budgets at a time of shrinking state and federal aid.

Dr. Phillip Callison (Los Angeles Public Schools): Right now, it's probably several million of dollars a year. Over the long run it will be equivalent of \$25 million a year of today's money.

Myers: But most say it's money well spent. About half of drug-exposed children who attend special classes at LA's Salvin school are able to successfully join regular kindergarten or first grade classes. In most cities, drug-exposed children are put in regular classes, getting little or no extra help.

Callison: What worries me the most is that the regular classroom teachers are not prepared to deal with these students.

Myers: Even with a little special training, this first grade teacher in Tampa struggled to cope with a drug-exposed child in her class.

Unidentified Woman: She will be hostile to class mates. Her attention span is extremely short.

Myers: Experts say the problem will get worse. One study warns that in a few years drug-exposed children may comprise as many as 60 percent of students in some inner city classes. For Today, Lisa Myers, NBC News, Washington.

Couric: Nancy Hamilton is deputy director of children's services for Operation PAR. That stands for Parental Awareness and Responsibility, a drug intervention program in Saint Petersburg, Florida. This morning, she's at our NBC affiliate in Tampa.

Nancy, good morning to you.

Nancy Hamilton: Good morning.

Couric: Tell us briefly about your program, what PAR is all about.

Hamilton: Well, Operation PAR is a comprehensive substance abuse program, education prevention and intervention. And we've had maternal substance abuse programs for about four years now. And, about--well over a year of our mother and babies residential program. And we've had some great success with the--with the children we've worked with. We've got some good strategies and some good techniques that work. We're concerned about the numbers because they are increasing. But we've got some good--good things that are showing great promise.

Couric: Nancy, you work with both the mothers and the children?

Hamilton: Yes.

Couric: Tell us what kind of problems these kids have, first as infants and later when they enter school, in general terms.

Hamilton: Well, they have a wide--they may have a wide range of problems. Going from nothing that you can see visibly to perhaps learning disabilities, some asocial behaviors, where is they have difficulty bonding with other human beings and getting along, and they may have severe problems. We've seen babies come from the hospital with enormous difficulties, digestive problems, respiratory problems, inability to focus, hypertonicity in their muscles, all the way from kids we can't see too much wrong with them, but we suspect that they may have problems as toddlers and as elementary school kids and definitely as adolescents.

Couric: An increasing number of experts believe that these kids do not make up a lost generation, that early intervention really can make a difference. You count yourself among those experts?

Hamilton: Yes. I'm really hopeful that--that if--if children and mothers are allowed the opportunity for treatment, we can do great things with them. My concern is that there aren't enough programs for mothers and children and that there isn't enough money. Our own program, we're concerned about next year and the year after, if we're going to be able to provide services for the mothers and the children.

Couric: What are your concerns about the children who go through the system and that the children people don't realize have a real problem?

Hamilton: That very much concerns me. Because as children go through life and--and they receive negative feedback from their environment, it affects their self esteem, it affects the way they see other human beings and how they can operate effectively and productively in life. And if they're not discovered and--and given some effective interventions, then I think they grow up feeling as if the world is a negative place, a hostile environment. And they treat the world that way. And we are very angry with them as they grow older and into their adolescence and commit crimes and wind up in prisons. And I think that we need to recognize that they probably should have been paid attention to very early on in their lives.

Couric: We only have a few seconds left, but--left, but the cost of educating and helping these children is enormous. How is the system going to handle this?

Hamilton: Well, I'm not too sure how they're going to handle it, but I know one thing, that the cost of doing it early on in their life is far less than the cost of watching these children grow up through adolescence and adulthood and the cost of...

Couric: Mm-hmm.

Hamilton: ...of taking care of them through prison systems...

Couric: Nancy Hamilton...

Hamilton: ...and special education.

Couric: Nancy Hamilton, thanks very much.

We're back in a moment with more on Today after these messages.

Bryant Gumbel, co-host:

Hey, the queen went to a baseball game last night.

Katherine Couric, co-host:

Hey!

Gumbel: She didn't have a hotdog nor peanuts...

Couric: Really?

Gumbel: ...or Cracker Jack, but we'll see what she did after a station break.

Bryant Gumbel, co-host:

Back at 7:25. More on the travels of the queen. Remember, we said she didn't eat beer and hotdogs? Would you like to know what she did eat...

Katherine Couric, co-host:

I would love to know.

Gumbel: ...at the ballgame?

Al Roker reporting:

Yeah.

Gumbel: You don't get this underneath the stands, by the way.

Couric: Sushi.

Gumbel: No--no. Maryland crab cakes, blackened smoked turkey...

Couric: Yum.

Gumbel: ...and chicken croquettes.

Couric: Mmm.

Gumbel: Buy me some peanuts and some chicken croquettes. No?

Roker: I don't care if I ever smoke a turkey.

Gumbel: Yeah. They said when--when a--you know, they brought the players down, they said when they gave--they were asked if they gave the players any special instructions about spitting and scratching in the presence of the queen.

Couric: Chewing tobacco?

Gumbel: You can tell the Orioles' spokesman was very sophisticated, he says, quote, 'I think players are sophisticated enough, they're not going to burp in her face.'

Couric: Charming.

Gumbel: Thank you--thank you very much, Bob.

Couric: They really know how to impress the gal, don't they?

Gumbel: Yeah, thank you very...

Couric: That's funny.

Roker: Yo, queen!

Gumbel: Have you--have you ever had any contact with royalty?

Couric: Um, no.

Gumbel: It is--it is kind of funny.

Couric: Is it?

Gumbel: Yeah. They give you--they give you special instructions on which you are and aren't supposed to do if they're around. They...

Couric: And--and your--the queen has to extend her hand to you?

Gumbel: That's right.

Couric: You never kiss her hand, right?

Gumbel: No. Don't kiss her hand.

Couric: Ever? Kiss her ring?

Gumbel: You don't bow. Don't bow. Also, the underlined this on the note, don't touch them.

Couric: Don't touch them?

Gumbel: No. Unless. If--I mean, like you don't go--you don't go...

Couric: She extends her hand...

Gumbel: ...let me tell you one.

Couric: Some lady yesterday in Washington tried to hug her. And, hug me, I'll show you what she did.

Gumbel: Oh, no.

Couric: She was like this. She wasn't into it at all.

Gumbel: Yeah, they--they tell you 'Don't touch them.'

Roker: So, no bonding?

Gumbel: No, no bond...

Couric: No. No body contact.

Gumbel: Years ago...

Couric: You can't do the lambada with her, either.

Gumbel: ...years ago, June--June and I had the--had the great honor of being invited to a cocktail party at the British embassy, a very private cocktail party for the princess of Wales--I'm sorry--yeah, Diana, Princess of Wales and Prince Charles. And there were only going to be, like, 30 couples there, 20 couples there, or whatever. And they made a big deal about it, they said, 'Look, when they--this is kind of like a cocktail party and they are just Mr. and Mrs. Smith,' you know?

Couric: Yeah.

Gumbel: And when they come in the room just meld, you know, just let them kind of meld.

Roker: Mingle.

Couric: Yeah.

Gumbel: That's right. Well, everybody was kind of--bzz-bzz-bzz--bzz--talking it up--when they turned the corner, dead silence. I mean...

Couric: Really?

Gumbel: Oh, yes. Dead silence. Everybody turned and looked--but it was interesting.

Couric: Well, did--did you speak with them? Were they nice?

Gumbel: Wound up speaking at--at length with them, yeah. And...

Couric: And what did you think?

Gumbel: Very nice people. I mean I...

Couric: I think Diana's a closet party animal, don't you?

Roker: Not closet.

Couric: I mean--you're right--you're right.

Gumbel: It was funny because, I mean the protocol even got to me so much that when it was done I got a call from somebody at the Washington Post who said 'We understand that you had an extended conversation with the princess,' and I said, 'Well, I don't know what you mean by extended.'

Couric: Oh, really?

Gumbel: And they said, 'Well, you talked to her for more than 10 minutes.' I said, 'That's probable.' Said, 'Well, what did you talk about?' I said, 'I think protocol demands that the queen--that the princess tell you, otherwise it's none of your damned business.'

Couric: You're so smooth.

Gumbel: I know.

Roker: Right!

Gumbel: Shut up!

Roker: You--you blighter!

Gumbel: I want to talk about Philip!

Roker: Grab him by his ears and shook him about! No! We're talking about the prince, you bloody fool! God save the queen!

Couric: What were you talking about?

Gumbel: It's--I'm not supposed to say.

Couric: Oh, come on. It's just us...

Gumbel: Honest, you're not supposed to say.

Couric: ...and a few thousand other people.

Gumbel: Honest. You know what was interesting, and June noticed this, she--I shouldn't even say that, I shouldn't...

Couric: Go ahead.

Roker: Come on.

Gumbel: But it was summertime...

Couric: And she wasn't wearing stockings.

Gumbel: Yeah.

Couric: She doesn't like wearing stockings.

Faith Daniels, anchor:

But she does shave her legs.

Gumbel: I didn't--didn't really explore that closely.

Couric: She doesn't like to wear stockings, apparently.

Gumbel: Really?

Couric: Yeah. Maybe that's shi-shi over in...

Gumbel: Is that right?

Couric: I don't know. Is it, Faith? Do you know?

Daniels: I've read that...

Roker: They drink warm beer, too. What do they know?

Daniels: If it were commonplace I don't think we'd read about it, and I've read about that, too...

Couric: Really?

Daniels: ...that she doesn't like to.

Gumbel: Yeah.

Daniels: You talked about kids.

Gumbel: I didn't think it was so bad. I mean she was certainly very nicely dressed. I mean I--in fact, I wouldn't have noticed it if June hadn't said something to me about it.

Daniels: You talked about kids. That's my guess.

Gumbel: Seven...

Roker: His lips are sealed.

Couric: He'll never tell.

Gumbel: I don't know. I mean I...

Couric: Don't even remember, do you?

Gumbel: ...what do I know about this stuff? We're back in a moment. Station break.

Bryant Gumbel, co-host:

Back now, 7:30 on a Thursday morning, here along with Katie Couric, I'm Bryant Gumbel. We have figured out that lawning is not a verb.

Katherine Couric, co-host:

No such verb.

Gumbel: But we tried.

Couric: No--yeah.

Gumbel: But neither is impacting and efforting and we keep on misusing those too.

Couric: And the one you invented a couple weeks ago.

Gumbel: That's right, but we don't talk about that one. Straight ahead in this half hour, we're going to talk about Mikhail Gorbachev and as the world tries to figure out whether

Gorbachev is, in fact, a liberal or a conservative, we're getting some help these days from a new book by a long-time Gorbachev watcher and journalist Robert Kaiser of the Washington Post. He'll be along in just a couple of moments. Katie:

Couric: And hold on to your briefs. Tonight's the big night for NBC's "LA Law," the season finale, a cliffhanger finish. And as we conclude our series on the show this morning, we'll meet the new members of the cast who all figure prominently in tonight's episode.

Gumbel: Hold on to your briefs?

Couric: You have a dirty mind.

Gumbel: Gene Shalit going to be--clean briefs, but Gene Shalit's going to be along in a couple of--of moments. He's in the Critic's Corner to look at "Switch" and "FX2." Let's get to the news desk right now. Faith Daniels:

Faith Daniels, anchor:

What do you do if you're wearing boxers?

Gumbel: Faith:

Daniels: The news.

Gumbel: Yeah.

Daniels: Yes.

Faith Daniels, anchor:

Secretary of State Baker is due back in this country tonight following his latest mission for Middle East peace. This morning, Baker held a final round of talks in Jerusalem, with Israeli officials, including Prime Minister Shamir. Later, he said there's still no agreement on the format of a peace conference or the role of the United Nations in it.

A three-hour standoff in Beverly Hills came to a sudden end during the night. A woman, armed with a handgun, killed one of the passengers before everyone else was able to flee. Later, gunfire was heard as police stormed the bus and killed the suspect.

Television viewers in the Soviet Union have something new--more of a choice. It's an independent TV channel in the Russian republic, promising news with a difference. Here's Jim Maceda.

Jim Maceda reporting:

It's already called "The Boris Yeltsin Channel." From the pre-revolutionary Russian tricolor and its logo, to Russian leaders, like Yeltsin, dominating its airwaves, it's clear that RTR, Russian Television, dares to be just that--the Russian republic's first independent channel.

Anatoly Lysenko (Russian TV, Through Translator): It's an affirmation of Russia's sovereignty and it's the first TV in the Soviet Union that's not influenced by the Communist Party.

Maceda: While it broadcasts from the Soviet TV center, its product is strictly alternative. Most of RTR's reporters and anchors were fired by Soviet TV, its controversial programs dumped by the national network. Journalists say the experiment in independent news is fun, and a challenge.

Alexander Gurov (Reporter): I never had a chance to work professionally in the western sense of word.

Maceda: Vesti, the 15-minute newscast, presents facts, not opinions. But the tone is satirical. On-air entertainment so far is mostly Gorbachev bashing. But even Yeltsin admits that can't last, that while it's very easy to criticize Central TV, now Russian TV must compete with it, and many Russians worry that it will be stopped before it even gets off the ground. Jim Maceda, NBC News, Moscow.

Daniels: At least three people were hurt during the night when tornadoes tore through parts of Western Oklahoma. Several homes there were damaged.

Police in Southern California are holding six people in connection with the seizure last night of one and a half tons of cocaine. The drugs were found in a Los Angeles suburb and are said to have a street value of almost half a billion dollars.

Latest from here. Now back to you.

Bryant Gumbel, co-host:

Faith, thank you.

Bryant Gumbel, co-host:

In planning her visit to this country, Queen Elizabeth expressed a desire to see something truly American. Well, her host complied with that request last night. NBC's White House correspondent Jim Miklaszewski has a report.

Jim Miklaszewski reporting:

It was the night that a part of America's past met America's pastime. Two of the world's most enduring symbols on the same field--the queen of England, and American baseball. President Bush brought Queen Elizabeth to Baltimore's Memorial Stadium for a game between the Orioles and the Oakland A's. It was the queen's first major league game. Seasoned royal watchers said she had the time of her life. She was so laid back she took off her gloves, in public, and the fans loved her. Even before the royal party arrived they were on their feet in anticipation.

Unidentified Woman: It's very exciting, very. Because it's fun to have the queen here! We've been to London. Now it's fun to have her come to Baltimore.

Miklaszewski: What do you think of the queen being here?

Unidentified Girl #1: Oh, it's awesome.

Unidentified Girl #2: It's great!

Miklaszewski: Why?

Unidentified Girl #2: I mean, because she came all the way from England and it's great.

Miklaszewski: Do you think she knows anything about baseball?

Unidentified Man #1: Probably not.

Miklaszewski: Do you know anything about cricket?

Unidentified Man #1: No.

Unidentified Man #2: It's like baseball.

Miklaszewski: What's that?

Unidentified Man #2: It's like baseball.

Miklaszewski: Cricket?

Unidentified Man #2: It is, I guess.

Miklaszewski: I can't believe--it's nothing like baseball.

Unidentified Man #2: Well, that's how much I know about it.

Miklaszewski: IRA protesters bought 100 seats in the bleachers, but they were orderly. The queen's presence even seemed to put some of the games biggest egos on their best behavior.

Jose Canseco: It's going to be exciting. Hopefully we can win and I'll hit a home run. I hope she understands the game of baseball.

Miklaszewski: The dugout was used for a receiving line. But these are guys whose only contact with the royals comes when they play Kansas City, so lessons in etiquette were a must.

Renee Lechemann (A's Coach): Of course, we know what to say, 'Hi,' to the royal highness, and we don't touch anybody until, you know, she talks to you, and then we--we're supposed to say, you know, nice things.

Unidentified Player: Liar. You just learned that.

Lechemann: So you're not supposed to shake her hand. You don't ask for autographs. But--so we'll--we're a very 'etiquetted' ball club under the direction of Tony LaRussa. But we'll talk to the president. We'll go ahead and say 'Hi, prez,' and 'We'll see you in the rose garden in November,' though.

Miklaszewski: The games biggest stars came away impressed.

Frank Robinson (Orioles Manager): It's very exciting. I'll still--my heart's pounding right now. It really is!

Reggie Jackson: It was wonderful. Meet the great lady of the world. It was great.

Miklaszewski: Some would say you're baseball royalty.

Jackson: Yeah, used to be.

Unidentified Man #3: Come on, guys. We want to get the game started.

Miklaszewski: And the game? It was average. The queen stayed for only two innings. The A's beat the Orioles 6-3. But it was still clearly one for the books. For Today, Jim Miklaszewski, NBC News, Baltimore.

Gumbel: Well now we've got another new one, along with lawning and impacting and efforting, we have etiquetteing.

Coming up on 7:37. Al Roker's gone outside to give us a check of the weather.

Al Roker reporting:

Well, I weathered my move down here to the Channel Gardens, Rockefeller Center, there's Prometheus. He looks pretty good. Just had a \$350,000 face lift with some gold leaf. (Weather follows.)

That's the latest. Now here's Katie.

Bryant Gumbel, co-host:

Good try, Al. Thank you.

Roker: Oops!

Bryant Gumbel, co-host:

In his seven years as leader of the Soviet Union, Mikhail Gorbachev has drastically changed that Communist state, but in the process of reforming his country, he's also brought it and himself to the brink of political collapse. Robert Kaiser of the Washington Post has long studied Gorbachev's policies and politics. His new book, "Why Gorbachev Happened," details the influences on and of the most dynamic world leader of our time. Bob Kaiser, good morning.

Robert Kaiser ("Why Gorbachev Happened"): Good morning.

Gumbel: How you doing? Welcome back.

Kaiser: Thank you.

Gumbel: This book is subtitled "His Triumphs and His Failure." Does it give away the ending a little bit? Is it certain that he's doomed to failure?

Kaiser: I--I--I'm looking for cover there obviously, but I--the failure that I have in mind is the failure to create in the Soviet Union a modern, thriving Democratic society. The society is spoiled, you know. Sixty years of Stalinism ruined that country, and it just isn't going to recover any time soon, and that's the underlying tragedy of this incredible experiment.

Gumbel: But--but, I mean, in admitting you're hedging your bets a little bit, you prompt the question of why now. I mean why--why come out with a book now before you're sure of what--why the final--what what the final chapter's going to be?

Kaiser: You know me, Bryant. I've been studying this country for 20 years, I lived there for three years. Watching Gorbachev happen, coming out of nowhere and changing his country and the world was so exciting for me and so entrancing, and I just decided a year ago at this time, I want to get a piece of this, want to get my two cents worth.

Gumbel: Yeah.

Kaiser: I have a lot to say. I've thought a lot about it, and I--when I started, I had no idea we'd be where we are today. In fact, when I finished most of the book last summer, it was still very upbeat. And then the things went sour in the fall, the terrible events in Lithuania and Latvia in January, and it has quite a different tone now.

Gumbel: Sure.

Kaiser: But it's--I just wanted to get my two cents in.

Gumbel: Your--your bet. How much longer can he survive, number one, and number two, if he goes, how goes the Soviet Union?

Kaiser: It's very hard, of course, to predict. This is one of the most dramatic stories either of us will ever cover, probably the most dramatic, and I'm not going to make firm predictions. My sense of what's happening now is power is ebbing away from Gorbachev and the whole central administration that he represents, ebbing to the republics, Yeltsin in Russian to the others in the other republics, and I think that is--that's the future. The--the--it's an artificial country, it was created by force, it's held together against the will of most of the non-Russian peoples, except in Central Asia, maybe, and--and they're gonna increasingly express their independent yearnings and act on them and I don't think the center and Gorbachev, or Gorbachev's successor will be able to prevent that.

Gumbel: Can--can Gorbachev be faulted then for being a short-term thinker, for not being able to see in advance that--that once he unleashed reform, in--in such pent-up volume in--in the Soviet Union, that it would outpace him?

Kaiser: Absolutely. I think Russian historians, a generation from now, will know more looking back, will fault him for never having a strategy. He always had tactics; he didn't have a strategy. He never really had in his mind, I don't think, a vision of what the Soviet Union he was trying to create would actually look like, how things would work, what people would do and how the government would work and so on. He's a maneuverer. He knew that the old system was lousy. He knew that it was built on lies. He knew that people didn't care about it. He knew that the society was literally alienated from the government. So he starts Glasnost, let's tell some truth, perestroika, let's shake it up, let's reorganize it. But he never had a, you know, a clear sense of where this was going and now it's going in many different directions at once, it's all messed up, and he's at a loss, I think.

Gumbel: Can he be faulted for--for too much becoming enamored of--of--of western opinion and trying to cultivate it?

Kaiser: I don't think that's a fair one. I--I mean, he certainly is enamored of the reception he gets in our world. He loves coming to Washington or London or Paris or

Bonn to get all those cheers, and he's used that very cleverly at home. But I don't think that's distracted him. I think it's been one of...

Gumbel: Didn't he become a prisoner of it in a sense, though, to the extent that--that he continued to court western opinion and has therefore limited his options in dealing with certain problems?

Kaiser: I think he'd say, if he was here, that it--it increased his options in the sense that if he had the support of Bush, as he has now, for example, he can get stuff out of us that he wouldn't get if he wasn't in--in that kind of a good relationship. I don't think he gave anything up, in other words, particularly.

Gumbel: You say his--his fatal flaw was his, quote, 'perceived mandate to redeem Lenin's revolution.' How so?

Kaiser: He keeps saying, right to today, 'I'm a convinced Communist.' He has something in the back of his mind that tells him that it's his job to--to make good on the Communist myths and promises. One--one of my arguments in the book is that he could only break up the old system the way he did because the party people trusted him. He was a party man and they recognized him as such and they gave him their confidence. But I think the fact he was a party man also limited him and at the crucial stage in the last six months when he was confronted, you remember the 500-day plan that was really change everything...

Gumbel: Sure.

Kaiser: ...he backed away from it, he chickened out, and I think it's because of this, because he couldn't see how this free market, really quite capitalistic system that the plan envisaged, could be called Communist.

Gumbel: Quick bottom line. Did he attempt the impossible?

Kaiser: Yes. He tried to create, out of a country that had really been despoiled by a rotten system for a long time, something terrific and new and it just didn't work as fast as he wanted it to.

Gumbel: Bob Kaiser, "Why Gorbachev Happened: His Triumphs and His Failure." Part two to come, I'll say.

Kaiser: That's right.

Gumbel: Bob Kaiser, take care of yourself. Always good seeing you. Seven forty-three.

Coming up later in this half hour, Katie's going to conclude her special series this week on "LA Law." First, we'll take these messages.

Gene Shalit reporting:

Good morning and welcome to the Critic's Corner.

The letters FX are movie slang for effects, special effects, and they are very special in the new movie called "FX2," directed by Richard Franklin and starring the appealing Australian Bryan Brown as a special effects man. His ingenious tinkering spills into his private life. Of course, things can go wrong. When you tinker, there's ever the chance.

This time things do go wrong. Result--murder. Brown's assignment--create special effects to effectively stop the bad effects the villain has on his victims. During a chase in a supermarket, Brown demonstrates how everyday items on the shelves can work in ways that their manufacturers never dreamed of. Although Bryan Brown is from down under, you know he'll end up on top, but the fun is seeing how he does it. He works handin-gimmick with a private detective pal, Brian Dennehy.

Dennehy has become one of Hollywood's most popular character actors, a second banana who's one of the best of the bunch. There are enough unexpected toys and tricky devices to make James Bond jealous, and they help to spin "FX2" into a clever thriller with a grin on its face.

Now here's a movie with loud laughter, "Switch." Blake Edwards has written or directed many memorable comedies, "Victor/Victoria," "10," "Breakfast At Tiffany's", the Pink Panther movies--combinations of sophistication and belly laughs.

Now Blake Edwards has another winner, "Switch," a classy comedy that slingshots Ellen Barkin into the rarefied ranks of reigning stars. Translation--if Ellen Barkin's on the theater marquee, it's a motion picture you have to see. So incendiary in "The Big Easy" and "Sea of Love," she now scores with a snazzy comedy performance, portraying a murdered man who's returned to earth as a woman--to teach him a lesson because his behavior toward women has been so macho crotcho.

While on earth, he skirted the issue. Now he's issued a skirt. Given this premise of a man's mind in a woman's body, Blake Edwards's dialogue zings the guy-ways and the sly ways of women and men, turning the genders upside down and inside out.

"Switch" rollicks with insights, out-of-sight slights and spoofs of the on-the-make mannerisms. Ellen Barkin's dandy sidekicks, Lorraine Bracco, Jimmy Smits, Jobeth Williams, and Tony Roberts, give her a leg up every step of the way. The center of "Switch" is loaded with wit, and "Switch" carries the letters, H-I-T. "Switch" is a witty hit.

And that's the Critic's Corner for this morning. This is Today on NBC.

Katherine Couric, co-host:

Listen up, "LA Law" fans. To get you ready for tonight's finale, we conclude our series on "LA Law" this morning with Cecil Hoffmann, Amanda Donoho and John Spencer, the new additions to the cast of "LA Law."

One of the highlights of this season was the introduction of three legal rookies to "LA Law." Amanda Donoho plays C.J. Lamb, a free-spirited lawyer who raised a few eyebrows when she hit on one of her colleagues at the firm--one of her female colleagues. John Spencer plays the chain-smoking street-smart Tommy Mullaney, an attorney who never quite learned how to dress for success. And Cecil Hoffmann plays the tough, yet vulnerable new assistant district attorney, Zoe Clemmons. (A clip is shown.)

What was your first day like on the set here?

Cecil Hoffmann: I was nervous, I was jet-lagged, I was--I worked with Harry my first show. He was the defense lawyer in a trial I was prosecuting, and I couldn't have had a better partner, you know, someone to just let me have my space, reassure me, answer stupid questions, tell jokes in long stretches of nothing to do. It was--you know, so I had

10 minutes of real fear, and then I was welcomed as if this space had been made and was waiting for me and they were glad I finally showed up to do it. It was really wonderful.

Couric: Let's talk a little bit about your character Zoe. First of all, is there anybody who's really named Zoe except for in a J.D. Salinger novel?

Hoffmann: I don't know. I actually don't know, but I think the most important thing about Zoe is that she's--she's so incredibly passionate about her work in an office that is so hard to work in. They've taken a story back into the DA's office where we haven't been for over a year. Part of her MO is that her heart has to be in it. It's not just about facts. It's about emotional truths and moral truths as well.

Couric: I cannot fathom that you guys were ever married.

John Spencer: Really?

Couric: I just--I don't see it.

Spencer: Isn't that interesting? I mean, I certainly can. I mean, from my point of view.

Hoffmann: Me too.

Couric: Because she's a fabulous babe, but you guys seem so different.

Spencer: Well, she's more than a fabulous babe. I mean, she's a provocative, intelligent politically astute woman who's nurturing and--and a fabulous babe. (A clip is shown.)

Couric: There's a lot of John Spencer from--the guy from Patterson, New Jersey in--in Tommy Mullaney, isn't there?

Spencer: No--I mean--sure--sure. I mean, yeah, and that's what's--that's what's wonderful for it for me, because it gives me--it gives me an opportunity to live in the space that--that I'm familiar with.

Couric: All right, Amanda, so, what's a nice girl like you doing in a place like this?

Amanda Donoho: Well, perhaps I'm not such a nice girl.

Couric: Perhaps not. Actually I'd like to rephrase that question.

Donoho: What's a naughty girl like me doing in a town like this? Well, where else would I be but Hollywood? It's--I think the cleverness of--of this show and of the people that run this show is they wanted to introduce a character who was unlike anybody else on the show and who would come up with some surprises. (A clip is shown.)

It's important that we deal with issues like this. It's important that actors like myself have the courage to say, 'Yeah, I'll do this. I'll do this because I believe that it's a correct thing to do, that it's an education, it's not sort of titillating or salacious.'

Couric: Are you disappointed that C.J.'s alleged or potential bisexuality isn't going to be further explored because it's just too controversial?

Donoho: I think that it's an unfortunate thing, of course, that there is still such a fear of material that's provocative, and sensitive as this, if you like. But I've had a great deal of

fun and--and taken an enormous joy in the responsibility of doing what Michele Greene and myself did with C.J. and Abby in the last few episodes.

Couric: We'll be back after this.

Bryant Gumbel, co-host:

We've only got time to say station break.

Bryant Gumbel, co-host:

Back now, it's 8:00, it's a Thursday morning, 16th day of May of '91. Straight ahead in this hour, on After Eight, the question is, what price green? The homeowner's dream of having a lush, greener lawn has led to a proliferation of chemical treatments that, in some cases, as we'll see, are proving to be life threatening. We're back in studio 3B on this Thursday morning. Along with Katie Couric, I'm Bryant Gumbel. As we talk about that lawn spot, we note that Joe Garagiola this morning is up the lazy river.

Katherine Couric, co-host:

Lawning.

Gumbel: Yes. He's busy lawning. He's up in the Hudson River valley with an alternative to putting chemicals on your lawn. Joseph, good morning.

Joe Garagiola, co-host (Claverack, New York):

Here I am, Bryant, American Gothic.

Couric: Where's your wife?

Garagiola: We--we have an environmental expert and I tell you, a lot of us are doing our lawns wrong. We're going to talk about that.

Gumbel: OK.

Couric: Thanks, Joe. Later in the hour, gadget guru Andy Pargh will be here with the latest in idiot-proof cameras. And we'll see what's involved in making your own frozen treats this summer.

Gumbel: And if you think you're having trouble selling your house during this recession, wait till you see Dennis Murphy's report this morning from jolly old England. Eight-oh-one. Let's move to the news once again. Faith Daniels:

Faith Daniels, anchor:

Thank you, Bryant. Hello again, everyone.

Faith Daniels, anchor:

Secretary of State James Baker wrapped up his Middle East peace mission today with little progress toward resolving the problems separating Israel and its Arab neighbors. Martin Fletcher is with us once again from Tel Aviv. Martin:

Martin Fletcher reporting:

Good morning, Faith. The peace mission has not ended in failure, the officials say. It just didn't get anywhere. After four meetings in 24 hours, there was a burst of optimism that maybe there'd be a surprise breakthrough. The word was Israel was ready to compromise. But when the meeting ended this morning, it was back to polite words and little substance. Baker said there were more areas of agreement than disagreement but the disagreements were in the two key areas. Israel still would not agree to a significant role for the United Nations in a peace conference and no agreement either on how long the conference would last. Those are the two problems that have bedeviled Baker since the start. Now Baker must decide whether to continue his peace mission and how. Shuttle diplomacy, at least for the time being, seems out. It's likely Baker will carry on, but with a lower profile. Faith:

Daniels: There's all this talk of--of the window of opportunity, Martin. Does that mean the window is closed now?

Fletcher: Well, Faith, the real question is was the window ever open. It's true the time was right for America to try, but it isn't sure the time was right for Israel and the Arabs to make peace. In the end it isn't what Washington wants that counts but what the enemies here want. To keep the peace process going now, Baker has to decide whether he wants to apply real pressure or not to make them want peace. Faith:

Daniels: Did Baker accomplish anything at all?

Fletcher: Well, it depends--it depends who you speak to. Actually he didn't really accomplish anything at all, no, because his aim was of course to convene a peace conference and he's far away from that. And the issues of agreement that he stressed this morning such as Palestinians and who represents them. Well, that was pretty much agreed on before he even started. So actually very little has been achieved, Faith.

Daniels: All right. Thank you, Martin. Martin Fletcher in Tel Aviv.

Faith Daniels, anchor:

President Bush may be on another collision course with Congress. The president Wednesday said he wants Congress to renew China's most favored nation status. But, as White House correspondent Jim Miklaszewski reports, Congress isn't likely to go along.

Jim Miklaszewski reporting:

At the White House, the president ticked off his reasons for renewing China's trade preference.

President Bush: I look at the support we got from China in Desert Storm. I look at the importance of China as a country and I think--I don't want to see us isolate them.

Miklaszewski: That sets up a confrontation with Congress. Many lawmakers want to rescind China's trade status.

Senator Daniel Moynihan (Democrat, New York): This nation, the People's Republic of China, is organizing prison labor--and they have a large supply of prisoners--to produce an export market in textiles.

Miklaszewski: Even the president has big problems with China. Its human rights record, arms sales to the Middle East and unfair trade practices. But White House officials argue that without the trade deal, the US wouldn't have any leverage whatsoever over China. In an attempt to appease Congress and pressure Beijing, the new trade agreement will be conditional on progress on political and trade reforms in China. The last time Congress challenged the president on China, Bush beat them, and the White House is confident he can do it again. Jim Miklaszewski, NBC News, at the White House.

Faith Daniels, anchor:

Two people were killed in Los Angeles this morning when a woman hijacked a city bus and shot a passenger to death. About 20 people were on the bus when the woman commandeered it. She opened fire, hitting one passenger. The wounded man fled the bus and was dragged away by police. He was later pronounced dead. The other passengers managed to get away as well. And after a three-hour stand-off, police stormed the bus, killing the hijacker.

Faith Daniels, anchor:

A Continental Airlines ticket agent is back on the job today. Continental fired the woman last week because she failed to follow company policy that women wear makeup on the job. The company says it was wrong in firing the woman.

Faith Daniels, anchor:

Well, it's spring and for most of us that means flowers, warm weather and longer days. But for the residents of Dodge City, Kansas, spring means moths, millions and millions of moths. Every year the moths migrate from the prairies to the mountains. Dodge City is one of the stop-overs. The insects pose no threat to humans or crops, they simply make being outside unpleasant. Visitors will be in the mountains within ten days. Unclear what happens to your clothes, though. It's 8:05. Time for Al Roker and today's weather.

Joe Witte reporting:

This morning's weather brought to you by Maxwell House Coffee. Always good to the last drop.

Al Roker reporting:

Excuse me. Well, they figure we--we had to rent this space for something, so they figured they may as well let me do a little lawning, as Katie would say. Only kidding, Katie. (Weather follows.)

That's the latest from Rockefeller Plaza. Back to Bryant and Katie.

Bryant Gumbel, co-host:

Al, thank you. You want to tell Al thank you for the lawning?

Katherine Couric, co-host:

Yes, thanks, Al.

Roker: You're welcome, Katie.

Gumbel: Eight-oh-seven. We're coming to come back in just a moment, talk about the controversy of what you may be putting on your lawn after this.

Katherine Couric, co-host:

On After Eight this morning: lawn chemicals and pesticides. Congress has been looking into complaints about domestic pesticides, and many lawmakers feel the price we pay for a green and weedless lawn may be too high. It may be costing lives. The fastest growing segment of this pesticide business in the past decade has been sales to commercial lawn care companies and homeowners. It's grown to a \$2-billion-a-year business. But reports of illnesses related to pesticides have been rising as well. It's suburbia's badge of honor, a lush lawn, a rolling carpet of green that reaffirms man's power over nature's destructive insects and outlaw weeds. It's a war waged after work and on weekends. Those without the time shell out dollars to companies which nurture and protect a patch of grass. But for some, it costs more than money to have a beautiful lawn. It's a threat to life. It's death by pesticide poisoning.

Chris Weidner: In November of '85 and in August of 1986, I had a miscarriage and both babies died exactly four days after my neighbors' lawns were sprayed and they both died in the same way.

Couric: Chris Weidner has since had a healthy baby. It wasn't until after she and her oldest son Ross ended up in an emergency room, struggling for breath, that it was diagnosed. They were poisoned by a commonly used pesticide called Dursban. Chris asked lawn companies to warn them before spraying in the neighborhood. It wasn't enough. They had to move.

Chris Weidner: I have to depend on the honesty of the companies that are making applications. Right now only some of the companies will let us know when they're making an application in the area. So if I don't get a call and I don't hear from anybody and they don't say that they're coming out, I can sort of take a chance and try to go outside and see if everything's OK. What they're saying is that you can walk on a lawn after it's been treated within an hour as long as it is dry. It doesn't seem to work like that for us. We're too sensitive to the products that are being used.

Couric: Chris cannot go outside without wearing her protective chemical suit. Malls and restaurants are off-limits unless her husband Bob determines that they are pesticide-free.

Bob Weidner: Well, it has taken a lot of spontaneity out of what we do. We used to, like, take trips and stop on the way and eat in a restaurant and now we have to go in and I go in first and ask if they sprayed any pesticides within the last 48 hours. In the beginning, it was--it was tough. It was, you know, a little weird to be walking down the street with someone with one of these suits on.

Couric: The Weidners founded GROW, an organization promoting organic lawn care. Getting the message out helps Chris feel less like a prisoner of pesticide.

Chris Weidner: My bars are glass bars. I resent the inability to go out and allow my children to play on their lawn. I resent the inability to be able to go to my own mailbox and get my own mail like normal people do.

Couric: Dr. Marion Moses is president of the Pesticide Education Center. She's best known for her work educating farm workers on pesticide hazards, and she's now turned

her attention to educating consumers. Warren Stickle is president of the Chemical Producers and Distributors Association. Good morning to you both.

Dr. Marion Moses: Morning.

Couric: Mr. Stickle, your association insists that lawn chemicals are safe. How can you give those assurances, especially considering what we just saw?

Warren Stickle: Well, we have to realize that many lawn care chemicals have been used for 20 or 30 years. So there's a long history of usage of lawn care chemicals without any adverse effects to human health. We're looking at a situation where each of these chemicals that are registered are extensively tested, and there's a lot of crossover chemicals insofar as 29 of the top 35 lawn care chemicals are also tested for food. So all of the higher chronic testing that needs to be done for food is also done for lawn care.

Couric: Dr. Moses, what do you think? I mean, the companies that actually sell them test them, and I wonder how reliable, first of all, that is. And the fact that they've been used for several years in your mind doesn't mean they're safe.

Moses: No. Absolutely not. Just because something is legal doesn't mean it is safe and I think the real problem with a lot of these chemicals is that they are a very, very serious health hazard. And I--I realize that the acute problems that people are concerned about, I think that's the tip of the iceberg. I'm much--much more concerned about long-term effects, and particularly in children and very young children and pregnant women and the fetus because there's evidence that they are at risk, certainly for--I'm very concerned about cancer in children. There are studies that show a relationship. And I think people say, oh, the EPA has tested it. People should be very aware. I think they should think about these people who purvey these products like used car salesmen and I think they should take a very serious look. These are toxic products. Their purpose is to kill and harm living things and we do not have the data that he says that shows that these are safe. They're not safe.

Couric: The EPA registration process, is that reliable?

Stickle: We think it is. And it's reliable in two ways. First of all, you register the product and then you have to go out and register it in each of the 50 states in which you are going to use it in. So it's a double--dual system here. The most important thing, though, is that we're going through a re-registration program at this point in time where--where we are re-registering all the old chemicals. The important thing about that is that the testing is being done and about 70 to 72% of the testing on those 29 lawn care chemicals has already been received by EPA. Now what kind of testing are we--are we really talking about? There are seven animal tests that are done for each and every chemical. There are two for cancer, two for birth defects, two for reproduction and--and the bottom line is that you're getting a lot of very important testing done on each of these products and the agency is working to complete that. And we're--we're on a timetable of the next five to seven years to get all this data in. And we think it's really important to reassure the public of that.

Moses: Well, you know--well, I think he's brought up a very important point that the public should realize. I think the people who sell these products have very economic concerns. They think it's a public relations problem. It's not a public relations problem. It's a public health problem.

Couric: Dr. Moses, I know you think better labeling should take place.

Moses: Absolutely. I think if the average homeowner and consumer knew what EPA knows about these products, they would not use them.

Couric: And you wouldn't disagree.

Moses: They wouldn't want their children exposed to them. They wouldn't want their pregnant wives exposed. They wouldn't--they wouldn't if they knew, and they don't know.

Couric: You think there should be better labelling as well?

Stickle: We think there should be better labelling. The label now is in really small print, difficult to read. It ought to be--it ought to be larger print. It ought to be streamlined and it ought to be easier to understand. The warning notices there should be clear. So the bottom line is the public does have a right to know and we really would encourage the homeowner to read that label very, very carefully before.

Couric: And you think there should be much more information in the labelling.

Moses: Oh, absolutely. I mean, to say we're going to put a label--we're going to warn you that we're spraying the chemical and it's a--it's a cancer-causing pesticide. What good does it do to warn somebody?

Couric: Quick answers. What's wrong with notifying people that you are spraying in an area?

Stickle: Well, many lawn care applicators now do that. They--and they put a postmark out there and post that they have notified people. Seven states also have a registry list where people who are super sensitive or have some kind of allergy...

Couric: Just seven?

Stickle: Just seven. And it's also not in the legislation now facing the Congress at this point in time. But people do have a right to know and if they are sensitive or allergic to a particular product, we think it's important that they do know. It's a question, though, of whether you notify everybody in a--in a housing development or you notify just those people who have a need to know. And I think that's the important point.

Couric: Dr. Moses, final word.

Moses: Everyone--everyone who uses a toxic product has a right to know about that. It's not a need-to-know problem. It's facing up to them being honest about the nature of these types of toxic chemicals that are making toxic lawns. They're dangerous.

Couric: Thank you both for joining us this morning. I'm afraid that'll be the last word. Joe Garagiola this morning is about 110 miles north of here, up the Hudson River valley, in the town of Claverack, New York with someone who knows all about organic gardening, which is an alternative. Joe, good morning.

Joe Garagiola, co-host:

Good morning, Katie. I'm with Larry Sombke. And you talk about toxic lawns, Larry, we've got a divet right here. How do I know I have a healthy lawn?

Larry Sombke: Well this--this lawn is healthy because it's got nice green lush grass on top, a very thin layer of--of thatch where the--where the lawn meets the turf. You've got a deep, crumbly--deep roots, nice crumbly soil, well aerated. There's probably worms in there, Joe. That's another good sign.

Garagiola: No chemicals.

Sombke: No chemicals. Your lawn doesn't need chemicals in the first place.

Garagiola: OK. I have a patch right here. I want to plant some healthy grass. What do I do?

Sombke: Well, first of all, dig it up. Dig out--dig up the area nice and deep. The key to an environmental lawn-care program is to work with the soil and let the grass take care of itself. So we worked in some organic material. We put some natural lawn fertilizer in there and then we raked it nice and smooth.

Garagiola: How can I test that it's good, the soil, though?

Sombke: Well, you dig some up and look at it. It needs to be crumbly. If you--if--if you can hold it in your hand and it looks nice and crumbly and it...

Garagiola: Don't you have experts that do this, though?

Sombke: Oh yeah. There are experts and you can test the pH level. That's one thing you have to do to find out...

Garagiola: I just have to buy this. I get it at the hardware store?

Sombke: You can get it at the hardware store or contact your Cooperative Extension Agency.

Garagiola: Put some grass seed on here for me.

Sombke: All right. Make sure you get the right grass seed. We don't want shady grass seed. We want sunny grass seed.

Garagiola: OK.

Sombke: So you get that out. Put a lot of grass seed on. Make sure you get the right kind of grass that'll grow in your area. There's northern grass and there's southern grass.

Garagiola: In Arizona I have to be careful.

Sombke: Right. You need things like bahia grass and different things like that. And then you--and don't be chintzy. You know, don't be cheap with grass seed.

Garagiola: OK. I got the grass seed. Now what do I do?

Sombke: Right. Put the grass seed on there nice and thick. Maybe sprinkle a little topsoil over that just to get it down.

Garagiola: OK.

Sombke: Put a little straw in there. And you use--you put the straw or hay on the top.

Garagiola: Man, if I did all that, I could grow hair.

Sombke: Yeah. If you just put a little--just a tiny bit of this on top, just to keep it from drying out. Gives it a better chance.

Garagiola: All right. Now what.

Sombke: That's a little thick right there. Then you grab a rake.

Garagiola: I'm rushing him through it because we want to get it all in.

Sombke: Grab a rake and kind of tamp it down a little bit. This is a clump. You don't really want that.

Garagiola: How about watering now? I see you've got something out there.

Sombke: With the water--watering is critical. You want to put nice, slow, deep watering. I've got a soaker hose going, and that's the best kind--the best kind of hose you can use...

Garagiola: I see.

Sombke: ...because it's water conserving, you don't waste water and it really does the job.

Garagiola: Now what are some of the things we're doing wrong as far as watering? Because that's one of the key things, isn't it?

Sombke: Well, you don't want to come home and sprinkle your lawn at night or as soon as you get home for 20 minutes. That's all wrong. What you want to do is a long, deep watering either with a sprinkler or with a soaker hose. The squirting it is bad. It develops shallow roots, which is bad for your lawn.

Garagiola: I picked a spot here, I think it's a bad spot. Is it bad?

Sombke: Well, we're going to find out. And the key to environmental lawn care is to look first and, you know, don't spray with chemicals first.

Garagiola: Are those weeds or flowers?

Sombke: Well, these--these--weeds are in the eyes of the beholder. These are flowers but I--I--some people consider them weeds so we're going to probably take those out.

Garagiola: What have you got here?

Sombke: This is a non-chemical treatment for grubs. Grubs is one of the number one lawn care insect problems. So instead of using a chemical pesticide we're going to use a bacteria called milky spore and we're going to just spread it on there.

Garagiola: Now with the dandelion, I don't want you to dig it out. I've got more important things. You just dig it out by hand, right?

Sombke: Dig it out by hand and don't mess with the chemicals.

Garagiola: How about mowing the lawn? We're doing things wrong, aren't we?

Sombke: Most people mow their lawn too short. They want it to look like a golf course. And that's wrong.

Garagiola: Why?

Sombke: Because once again you have a real short grass. That means you're going to have shallow roots and you've going to have a hard time keeping your grass healthy. You want to cut your grass a little bit longer, about two inches or so.

Garagiola: Like Kathy's doing. And you want to leave the...

Sombke: Leave the grass clippings on the lawn. They can provide up to 50% of your fertilizer needs. Also grass clippings are the number one source of trash in the United States. Don't send it to the landfill. Leave it on your lawn.

Garagiola: OK. That's a pretty good lesson for you in how to grow a healthy lawn, Katie, and I know you want to do it because Bryant's got a healthy one.

Couric: Absolutely. My goal in life, Joe. And I want you to get out and help--help Kathy with that lawnmower.

Garagiola: I will. Kathy's doing a good job.

Couric: OK. Thanks, Joe. We're back in a moment with more on Today after these messages.

Bryant Gumbel, co-host:

The latest in cameras after a station break.

Bryant Gumbel, co-host:

Back now, 8:25. Faith was just reprimanding me for trying to be my own doctor on illnesses. I mean, when you're sick, you don't always go to a doctor, do you?

Faith Daniels, anchor:

Not always, but there's a point.

Gumbel: What's the point?

Daniels: After spending two days off work in bed, I think that's a point.

Gumbel: I don't know. I mean, I--I think I know what I have. So...

Daniels: What is that?

Gumbel: I think I have another case of tonsilitis.

Daniels: But tonsilitis...

Gumbel: Remember we looked at each other's tonsils on the air that day? I've still got mine and mine act up every now and then and I don't feel compelled to go to a doctor to have him tell me you have tonsilitis.

Daniels: Maybe you should have them out.

Gumbel: No, I'm not going to have them out. That is terribly painful.

Katherine Couric, co-host:

Really, really painful for an adult.

Gumbel: Yeah.

Couric: Painful for a child even more so.

Gumbel: Yeah, but they're too young to remember it, right?

Couric: I remember when I had my tonsils taken out.

Daniels: How old were you?

Couric: I think I was seven years old. They were infected and the poison was dripping into my stomach so I was constantly throwing up. Isn't this attractive? So finally, they thought I was going to die. They took me to all these doctors and hospitals. They couldn't figure out what was wrong with me. I went to one pediatrician. He said your tonsils need to be taken out. They're infected. And it was--it was really painful afterwards, you know, for several days.

Daniels: All this is making me sick. Excuse me for coughing.

Gumbel: I got to tell you. June had hers taken out not long ago. When I say not long ago I'm talking about within the last 10 years, all right? And watching her deal with that, I decided not a chance, not a prayer. I mean, I'll put up with this every other year or so when it gets infected.

Daniels: But you could have strep.

Gumbel: I could. And then what?

Daniels: They have to treat that.

Gumbel: And then you could be giving me strep.

Daniels: Now there's a point.

Gumbel: Well, I'm doing my best not to cough in your direction or anything else.

Couric: Yeah, you haven't kissed me much this morning.

Gumbel: Nah, not really. Just on the lips. No big thing. But, I mean, I just don't feel compelled to go to a doctor to have him tell you what you already know.

Daniels: I think men are like that. Men will go to bed for a week but they won't go to a doctor.

Gumbel: They won't ask directions, either.

Daniels: No, they don't.

Gumbel: What is that? Wait a minute.

Couric: It drives me nuts.

Daniels: It does.

Couric: Every time I'm lost with Jay I'll say, look, there's somebody there, they--you know, they'll be able to help us. He goes, no. Men have this thing, they want to find out for themselves how to get to a place. And women are very quick to ask people directions. Don't worry, Bryant.

Daniels: Dean was lost for an hour. He was supposed to meet me for dinner. Lost for an hour and didn't call for directions.

Gumbel: Strength. Give me strength.

Couric: It's true though, Bryant.

Gumbel: It is not true.

Couric: You don't ask people for directions, do you?

Gumbel: What generally happens...

Daniels: They might tell him where to go.

Gumbel: What generally happens when guys travel with their wives to places they don't know where there's--places they've never been before, generally they hand their spouse the directions...

Couric: Oh, then they're the navigator.

Gumbel: ...and say, you be the navigator. And generally the spouse sits there and after you have passed they go, 'oh, you were supposed to make a left back there.' That's what generally happens. So don't talk to me about asking directions. That is what happens more often than not.

Daniels: Dean would probably agree with you on that.

Gumbel: No, I mean, that's--that's the way the game goes.

Daniels: My dad--my dad was always willing to stop and ask directions, but, he would--from the time he walked in the gas station to the time he came back to the car he would forget them and then be too embarrassed to go back in. So he would drive to the next gas station and ask again.

Unidentified Man: Some people who work at gas stations nowadays don't know the directions.

Gumbel: Yeah, that's right. That's another problem.

Couric: That's true.

Gumbel: You go to a gas station now you've got no, no luck at all.

Couric: Yeah. Oftentimes they don't even speak English, which makes it even more difficult.

Daniels: Don't you love when you stop someone on the road and they pretend that they know and yet when you take--when you follow it they have no...

Couric: Oh, I've done that before. When people have stopped and asked me directions to a very simple place--and I've lived in Washington all my life and I really should know--so I'll say, yeah, it's that way. Just go about two miles. And then they'll leave and I'll say, I have no idea what I just told them and I just lied to them.

Gumbel: We had a guy--we were...

Daniels: That's mean.

Couric: Well I didn't--it was when I was younger.

Gumbel: We were in Atlanta one time, asked for directions, guy turns to me, he goes very simple to get there. He says, you go to your second light and you turn left. And he repeats the directions. And I didn't want to embarrass him by saying, hey Bozo, you pointed right. So I said, let me--give me that one more time. He says, yeah. Go to your second light, then you turn left. And I said, I go left, or I go that way. And he goes, yeah, you go left. I thought, this is terrific. At that point I said, June, read them better. We're going to come back in just a moment. Very nice, Giusep.

Joe Garagiola, co-host:

You need help, Bryant.

Gumbel: Yeah. Are you stuck in that position or what?

Garagiola: Watch.

Gumbel: Station break.

Garagiola: I can swing with...

Bryant Gumbel, co-host:

Back now--oooh! Isn't that artsy? We're back at 8:30 on a...

Katherine Couric, co-host:

Except we're being covered by the...

Gumbel: ...Thursday morning.

Couric: ...sun.

Gumbel: Well, it is kind of the sun roof in the--in the studio. That is a very nice effect there. Who got that one? Robes or Bucky? Is that a--oh, it's under Bucky's guidance.

Crew, off camera: No!

Gumbel: We are told that Robes was nothing but the tool. Anyway. Straight ahead in--in--in this half hour, we'll talk of putting up your house for sale. It is never easy. As we will see in just a couple of moments, it is even more difficult in jolly old England for the landed gentry. Katie:

Couric: And if you're like me, all thumbs when it comes to operating gadgets like cameras, you'll be very interested in what gadget guru Andy Pargh has to show thi--show us this morning in cameras that are painless to point and shoot.

Gumbel: You are a big ice cream fan, yes?

Couric: Yeah. I like ice cream.

Gumbel: Al Roker...

Couric: You...

Gumbel: ...I'm sure will be running back up here to taste this too. We got an ice cream spot before you get away this morning. Let's move to the news desk right now. Faith Daniels:

Faith Daniels, anchor:

Thanks, Bryant.

Faith Daniels, anchor:

Secretary of State Baker reports to President Bush tomorrow on what appears to have been another fruitless peace mission to the Middle East. Baker left Israel today after one last meeting with Prime Minister Yitzhak Shamir, Foreign Minister David Levy and Defense Minister Moshe Arens. They appeared to have made little progress toward an agreement on key issues surrounding a Middle East peace conference.

A three-hour standoff came to an end in Beverly Hills, California, this morning as sheriff's deputies stormed a city bus and killed the armed woman inside. It was the end of a standoff that began with a shooting incident aboard the bus. Police say the woman had opened fire, killing a passenger. About 20 other people managed to escape from the bus as it rolled to a stop at a busy intersection.

The public-service announcements say that if you're not recycling, you're throwing it all away. Because of marketing problems, some recyclers may be forced to throw it all away anyway. More from Scott Miller of KING-TV in Seattle.

Scott Miller reporting:

Recycling is getting easier and easier. In more and more American cities, you can now recycle right at your curbside. But it's not always easy for contractors to get rid of this stuff, especially scrap paper. Here in Washington, state most scrap paper is shipped to Asia and now bales are filling up warehouses up and down the West coast because there is no way to get them across the Pacific.

Don Kneass (Recycle America): We're going to keep storing it up. I mean, the next option for us is to begin storing it outside and hope it doesn't rain.

Miller: The problem is a worldwide container shortage. Many of them are still tied up in the Persian Gulf, filled with war supplies. Scrap paper isn't worth much and the containers are available are getting filled up with the highest value exports. If the backup keeps getting worse, some recyclers may have to haul their paper to a landfill.

Ed Steyh (Seattle City Utility): They cannot continue to store material and not be able to get rid of it.

Miller: The container crunch is expected to ease up in a few months, but experts say the ultimate solution is to find a domestic buyer for the scrap paper people so dutifully toss into the recycling bin. Scott Miller, for NBC News, Seattle.

According to a presidential advisory commission, an agency that safeguards Americans' health is in critical condition. The panel says the Food and Drug Administration has too much work to do with too little money and too few people.

Queen Elizabeth's visit to the United States is hitting a high note today. She's becoming the first British monarch to address a joint meeting of Congress. Last night, she was introduced to baseball royalty as President Bush's guest. After meeting the teams, the queen sat in on two innings of the Orioles-Oakland A's game in Baltimore.

Later today on "A Closer Look," the ultimate survivor: Elizabeth Taylor. After seven marriages, six husbands, problems with drugs, alcohol, illness and her weight, she's still the woman that people want to talk about. We'll talk about her with former husband, Eddie Fisher, and a former co-star, Mickey Rooney as we continue our look at America's uncrowned royalty.

Faith Daniels, anchor:

Eight thirty-four now.

Bryant Gumbel, co-host:

What do you think the queen found so funny there? She was, 'Ha, ha, ha, ha.' Thought she watched the...

Katherine Couric, co-host:

Something witty the president said.

Gumbel: Oh, I thought it was something that happened on the ball field. She wanted to watch somebody field a ground ball or whatever. She was, 'Ha, ha.'

Daniels: A little scratching.

Gumbel: A little royal laugh there. Let's--eight--eight--8:34. Go on down to the Channel Gardens. Wonder why they are called that? Anyway. Al Roker is down there doing business.

Al, why are they called the Channel Gardens?

Al Roker reporting:

Oh, uh, well, the Channel Gardens? Well, I--I guess, because they're on TV, Bryant. In any event, we've got--sorry. It's--I don't know. In any event, they--we are in the Channel Gardens. It is a--it is a woodland--woodland flower exhibit here. That's all made of cedar. There are some 60,000 plants in here and all in all it's looking pretty nice. And we hope it's looking nice around your neck of the woods. (Weather follows.)

Willard's back tomorrow and save some of that cookies and cream ice cream for me, Bryant. I'm coming back.

Gumbel: Hey, Al, before you disappear...

Roker: Yeah?

Gumbel: ...we have an answer on why they are called the Channel Gardens.

Roker: And that is?

Gumbel: Because to your left right now is a British building and to your right is the French building. So obviously between them, the channel.

Roker: The channel!

Gumbel: Da-da!

Roker: Well, I'm going to make--I'm going to go under the channel and come back upstairs in just a minute.

Gumbel: OK. All rightie. Thanks, Al. 8:36.

Bryant Gumbel, co-host:

Our Over There segment this morning takes us to the lake district of England, where "Today" foreign editor Dennis Murphy has a report on a family's parting with a centuries-old homestead.

Richard Bigland: Well, it is true that the house and the estate is for sale. Now the modern--with modern day pressures the estate has had to pay for itself. This has been really--really difficult.

Dennis Murphy:

The Biglands have been living on these thousand acres for more than 800 years. But now, the recession and stiff inheritance taxes have forced Richard, Kate and the Bigland children to put the ancestral home on the block.

Richard Bigland: We have always known ourselves to be the old--oldest English family living in our own patch. We're looking out at the direction that the Vikings would have come here in the first instance, and they would have come swinging up Morecambe Bay there and seen this hill from a distance. I guess everything would have been just as it is today over 800 years ago.

Murphy: And now Bigland Hall will pass on to someone else. The fireplace built in 1161 and all those portraits of Viking's descendants.

Richard Bigland: Many, many, many Bigland portraits look down at you wherever you go. As you go up the stairs they all frown at you or smile at you, depending on what sort of mood you happen to be in.

Kate Bigland: It is the most extraordinary setup. It is like living in a novel in a funny way. I mean, it is very odd for people--you know, for one family to stay for so many years.

Murphy: Richard thinks one family member is still here.

Richard Bigland: The house has got a ghost. I'm not sure whether it's a good thing or a bad thing to tell people. All the villages here, everybody knows about the White Lady at Bigland Hall. I can remember in the noise of her dress which was dragging on the stairs because it was a long dress but when I looked around, she wasn't there. I had just seen the White Lady.

Murphy: Richard tried to make a commercial go of the lake, fishing, wind surfing, but nothing panned out. The estate is just too large for one family to manage these days.

Richard Bigland: Bigland was never a place that one made one's money at. It was a place that one--one enjoyed when one felt that one liked to be quiet and away from it all.

Murphy: There was a Bigland who made it big in America, George Bigland. He started the Pony Express and was a founder of the Mormon Church.

Richard Bigland: He was a blood brother of the--of the Sioux Indians. And he--when--when he did come back to England, he brought quite a lot of his relics with him. And George is the one in the jacket. And in fact, that very jacket of George's is still here that he used to wear, with tassels and all. And as a child, I used to wear that too, sadly. I say that sadly because maybe it might have been in slightly better order. I don't know.

Murphy: These are reflective days at Bigland Hall.

Richard Bigland: I have thought about this at great length. The last six months of my life here have been dreadful. Debating things like, 'How could you possibly do this? You, Richard Bigland, after 866 years? How could you sell it? How could you get rid of it?'

Kate Bigland: For Richard, I'll feel quite sad, but for the sake of the kids, they'll grow up in the real world, rather than a very protected environment, which actually this is.

Richard Bigland: The sadness is that unless, of course, the future purchaser of this place changes his name to Bigland, there won't be a Bigland living here any more, which is a real shame.

Murphy: For "Today," Dennis Murphy, NBC News, London.

Gumbel: Coming up on 8:40 on this Thursday morning. Katie is back in just a moment to talk cameras with the gadget guru, right after this.

Katherine Couric, co-host:

Years ago, finding an easy-to-use, high-quality camera was a real shot in the dark. But today, with all the inexpensive hi-tech electronics available, even the most basic camera will more often than not give you terrific, goof-proof pictures. Our own gadget guru, Andy Pargh, is here this morning with all kinds of ways to preserve that special moment. Those times of your lives.

Andy Pargh (The Gadget Guru): Oh, they are and you know, they are getting not only easier to use but now cameras are taking better pictures than ever.

Couric: Well...

Pargh: I'll give you an example. You know, nobody likes to get their pictures back from the processor with red eyes. Today's cameras have new circuitries and designs that re--reduce red eye to an all-time minimum.

Couric: This guy has red eye.

Pargh: He has red eyes. It was not...

Couric: Red pupils.

Pargh: ...taken it with one of the--with one of the cameras we have here--here today. Basically what causes red eye--when the flash goes off, you know, in--in your face it illuminates the blood vessels in the back of your eye--in the back--in the retina. That's all you are seeing, illuminated blood vessels. So some camera companies such as Olympus has a camera like this one--if you'd like to take a picture. What it does is right before the flash it will burst about 20 or so--20 to 30 strobes.

Couric: Smile, Bryant.

Pargh: So the strobes are designed to reduce the pupil size. Let's see. It--it's funny. We are under the lights, so the flash didn't go off here.

Bryant Gumbel, co-host, off camera:

Where's the strobes?

Couric: Oh.

Pargh: We have to do it a little in the dark here. Bring it down. I guess the problem is we have too much light.

Couric: Oh, that's OK. We'll do the strobes later...

Pargh: See, this--this--this camera is extremely smart...

Couric: ...in the dark.

Pargh: ...and it knows when, you know, when it does not have enough light for the flash.

Couric: It is smarter than we are, huh?

Pargh: It really is.

Couric: OK.

Pargh: But this does have a strobe. You will just have to trust me on that one.

Couric: OK. Now they...

Pargh: But this is the Stylus from Olympus.

Couric: ...saying try it because they've...

Pargh: OK.

Gumbel: Turn the lights down.

Couric: ...dimmed the lights, Andy.

Gumbel, singing: When the lights go down low.

Pargh: Oh. We'll try it over here. We are not getting it. Too much light.

Gumbel: Nice camera, Andy.

Pargh: When the pictures come back we'll see if it works.

Couric: It really does work, ladies and gentlemen. OK. What's next?

Pargh: But--but that's the Stylus from Olympus. It sells for \$225. Now one thing that's important to note about cameras--today I will be quoting suggested retails. All cameras can be found for about 25 to 40 percent less than suggested retail. They are extremely discounted items. This...

Couric: At various stores around the country?

Pargh: At various...

Couric: OK.

Pargh: Yeah. I would go discounters, catalog showrooms, those type of places...

Couric: OK. Great.

Pargh: ...are your best camera deals. This camera, the Kodak star 935, removes the flash from the lens and that is their method of reducing red eye. This unit sells for about \$80.

Couric: Well, that's good.

Pargh: OK. And...

Couric: And this is an idiot-proof camera?

Pargh: Yeah. That is real idiot-proof. You put the film in and you go. Now one of the more unique cameras this year is--this is the Fuji Discovery 3000. It sells for about \$430. But this has one of my--my favorite features I've ever seen. It's called auto rewinding. And I know--let me ask you a question. Have you ever accidentally or inadvertently opened the back of a camera and exposed a roll of film?

Couric: You know, I have, Andy, and I hate when that happens.

Pargh: Well, it's--it's--it's--it's horrible.

Couric: And this...

Pargh: With auto rewinding, it won't because what it does--as soon as you load the roll, it automatically advances it to the end of the roll and then takes the pictures backwards. So as soon as you've taken the picture, it goes inside the canister where it's safe.

Couric: You're saying this one is for real idiots?

Pargh: This is--Katie--Katie, try it on for size.

Couric: OK.

Pargh: But it also--it has a dual flash.

Couric: I'll take you this time, Andy.

Pargh: OK. It has a dual flash system on there. One flash is for your preflash and the other is for illumination and a great camera. It's--it's--it's not like a pair of binoculars.

Couric: Is this an auto focus?

Pargh: Yes, it is auto focus.

Couric: Because Bryant is looking pretty blurry right now.

Gumbel: Pink-eyed, right?

Pargh: OK. What--what you do--put your finger down on the button one time. That will put it in focus.

Couric: OK. Cool.

Pargh: And go from there. Oh, did you...

Couric: I think there was something in front of the camera but who knows, Andy? We'll see...

Pargh: I think your finger was...

Couric: ...when we--when I get it developed.

Pargh: ...right in front of the sensor, but...

Couric: OK. No problem.

Pargh: ...you know, a little bit of practice and you should be...(unintelligible)...

Couric: OK.

Pargh: Now this Photosure from Canon--now Bryant said this was his favorite camera out here. Other than just its unique shape and--and style with the zoom lens, it has an infrared remote control where--to turn power off and on. OK. Let it reset back here. We will give it just a moment--and it doesn't want to work for us right now.

Gumbel: It worked earlier.

Couric: But it...(unintelligible)...really works.

Pargh: We are batting 1,000 right now.

Couric: It did...

Gumbel: But show how the lens cap has the...

Pargh: OK. And...

Gumbel: ...thing there.

Pargh: One of the--the flash is built inside the lens cap and it conceals right there. This unit sells for about \$545, has a caption mode on it and it's new from Canon.

Couric: That's pricey.

Pargh: Do you want to see something really unique. Put this one--let's turn it on first.

Couric: Good idea.

Pargh: OK. And let's--let's put this right up to your eye and see what happens. This has an...

Couric: Oh, wow!

Pargh: ...infrared sensor by your eye. As soon as...

Couric: It automatically...

Pargh: ...you put it up, it automatically...

Couric: ...zooms in.

Pargh: It--it frames your subject. So it makes it even easier. It still has a 35 to 105...

Couric: Oooh! Makes a lot of...

Pargh: ...zoom lens...

Couric: ...weird noises.

Pargh: ...and it does have the red eye reduction. The dual flash.

Couric: Right.

Pargh: And that's new from Minolta.

Couric: A--a must. OK.

Pargh: OK. Now, loading film.

Couric: Oooh! OK. All right.

Pargh: They make lots of noises. Loading film. This is the Fuji mini-dual date drop-in film loading. It doesn't get easier than this. The film is loaded.

Couric: Oh, great! So you don't...

Pargh: This you...

Couric: ...even have to line up the little...

Pargh: You don't have to open it up.

Couric: ...perforations.

Pargh: And this also has the auto rewinding.

Couric: Cool.

Pargh: So it's going to the rear of the roll right now.

Couric: OK. Will it just do it's thing...

Pargh: It just keep on going.

Couric: ...and just move on.

Pargh: Now if you have ever gone to a party, don't you hate to be the one who is stuck taking the pictures? Well, this is Konica's new Compie and what this does--it has a microphone inside here and it listens for bursts of sounds...

Gumbel: Yo!

Pargh: So what we'll do, we'll go, 'Hello.' And what it will do--it listens for bursts of sound such as laughter.

Couric: Hey! We are having so much fun. Take our picture. See, there you go.

Pargh: And it--it takes the pictures and then it automatically pans 100 degrees to get another shot.

Couric: And do the little...

Pargh: So you can put it in the corner of a party...

Couric: ...saddle shoes come with this, Andy?

Pargh: Yes, they do. Those are not sold extra.

Couric: Very attractive.

Pargh: They only come in brown and white.

Couric: OK. Now these are di--let's quickly.

Pargh: OK. We...

Couric: Disposable camera.

Pargh: ...we have single-use cameras. They're disposable. They come in a wide variety. You have, for example, the weatherproof one which is--can go seven feet under water, sells for about \$15...

Couric: OK.

Pargh: ...to the stretch cameras...

Gumbel: You promise to take a picture of this for me?

Pargh: ...which sell for about \$15. And we just have a couple of examples here. The stretch cameras are the ones that you get the wide panoramic shots.

Couric: OK. Great. Andy, thanks a lot.

Pargh: Thank you.

Couric: Thanks for giving it a shot. Get it? Don't go...

Pargh: Oh. That's a good one.

Couric: ...don't go away. We've got ice cream coming up. This is "Today" on NBC.

Bryant Gumbel, co-host:

With the temperatures climbing into the 80s this week, we thought it a good excuse to get in an ice cream spot. We invited Debbie Lawrencels to join us here in-studio. She is a recipe developer for Haagen-Dazs.

Debbie, good morning.

Debbie Lawrencels: Good morning.

Gumbel: What does a...

Lawrencels: Thank you for having me.

Gumbel: ...recipe developer do? Give me a job description first off.

Lawrencels: Well, I sit and I play with ice cream all day. I make a lot of different recipes.

Gumbel: They pay...

Katherine Couric, co-host:

Sounds fun to me.

Gumbel: ...they pay you for this?

Lawrencels: I pay--get paid.

Gumbel: OK.

Lawrencels: I actually just make a lot of recipes and train people how to make them.

Gumbel: Train Katie.

Lawrencels: Which is why we're here today.

Gumbel: What is Katie going to make?

Lawrencels: We are here today--you are going to make a yogurt fruit shake.

Couric: Yee haw!

Lawrencels: A delicious yogurt fruit shake.

Couric: OK.

Lawrencels: I'm going to ask you to take this scooper and then scoop a nice big scoop. Oh, you need more than that.

Couric: OK. It's a big...

Lawrencels: Yeah. This is a low-fat product though, all natural. And we're going to put more in. Great. That's great. Even more.

Couric: I used to do this, you know, when I worked...

Gumbel: Oh, sure you did!

Couric: ...in the su...

Lawrencels: You're doing great--you're...

Gumbel: It's obvious.

Couric: I--I used to be a...

Lawrencels: OK. That's enough.

Couric: Is that enough? OK. Good.

Lawrencels: That's plenty. That's great. So, now you're going to add some milk. We're going to add some skim milk...

Couric: Skim milk. Good.

Lawrencels: ...to keep it a little bit...

Couric: We want--this is a healthy ice cream confection if you didn't notice.

Lawrencels: Healthy. Very good in potassium. We're going to--we're going to add some bananas...

Couric: Bananas.

Lawrencels: ...here. We're ad--adding one banana. This is going to make a portion for two.

Couric: OK.

Lawrencels: We're going to add some strawberries.

Couric: Some strawberries.

Lawrencels: Three fresh strawberries and of course you could substitute any fruit that you like.

Couric: Like blueberries. I like blueberries and peaches actually.

Lawrencels: Sure.

Couric: Now...

Lawrencels: And now, this is just a little bit of...

Gumbel: Vodka!

Lawrencels: ...syrup we're going to add.

Gumbel: Oh, syrup. I'm sorry.

Couric: Oh, this is corn syrup. But I would rather not put that in. Do I have to?

Lawrencels: No, you don't have to.

Couric: Because it is just added calories, Debbie.

Lawrencels: That's true. OK.

Couric: All right. Now what do we do?

Lawrencels: Very few calories, but it sweetens the strawberries a little bit, but that's OK.

Couric: But I think that's sweet enough.

Lawrencels: That's great.

Couric: OK.

Gumbel: Strawberries are going to be bland if you don't put some.

Lawrencels: That's fine.

Couric: No. It will be fine.

Lawrencels: That's fine.

Couric: Just you wait.

Lawrencels: Now...

Couric: OK.

Lawrencels: Got to make sure it is on good and tight.

Couric: OK. Ready? Let her rip!

Lawrencels: We're going to put that on for 20 seconds. Let it rip!

Couric: These are--these are great for breakfast. I do this for breakfast a lot.

Lawrencels: Great.

Couric: OK.

Lawrencels: OK. You can turn it off.

Al Roker reporting:

You could even put bacon and eggs in there, couldn't you?

Lawrencels: OK.

Couric: Sometimes I use just regular yogurt too instead of ice cream, you know...

Lawrencels: This is delicious.

Couric: ...instead of frozen yogurt, rather.

Lawrencels: This is absolutely delicious.

Couric: OK.

Lawrencels: This is actually less than 270 for the cup.

Couric: Whoops.

Lawrencels: Ooops.

Couric: Didn't quite blend it all, did I?

Lawrencels: OK.

Couric: OK.

Lawrencels: That's beautiful and you're going to garnish it because that makes nice summer entertaining.

Gumbel: Oh, what a garnish!

Couric: Isn't that pretty?

Lawrencels: That is very lovely.

Couric: There you go. Voila. Put a little straw...

Lawrencels: And a little straw.

Couric: ...there and we're good to go.

Gumbel: Taste...

Lawrencels: And why don't you take a sip?

Couric: OK. It's good but that big glob is stuck in the straw and so I really didn't get any. So...

Gumbel: All right.

Couric: ...keep--you guys go on.

Gumbel: Debbie--Debbie, before I cook, what is the worst recipe you ever tried to come up with?

Lawrencels: Oh, I think champagne with grapes and yogurt.

Gumbel: It didn't sell?

Lawrencels: No. Well, we didn't make it for the--you know, we had--we had been practicing and testing for home use and...

Gumbel: OK. What am I making here?

Lawrencels: OK. You are making a banana split. A classic...

Couric: All right.

Lawrencels: ...banana split. Here is your banana and what we're going to ask you to do is hold that in the palm of your hand. You can leave that peel right on there.

Gumbel: You're kidding. I eat the peel too?

Lawrencels: You-we are going to cut it fancy. We're going to make it into quarter inch slices...

Couric: Roughage.

Gumbel: Oh, just quarter inch.

Lawrencels: ...like this. Yeah.

Gumbel: This is trouble.

Lawrencels: OK.

Gumbel: Oh, like this!

Lawrencels: And you can put it right into the dish, but you're only going to put in half because you want a good eating experience. You want half of the bananas at the bottom. That's great. Now you can...

Couric: Look how gingerly he's slicing that.

Lawrencels: ...put that down. That's beautiful. He is an expert master...

Gumbel: Obvious.

Lawrencels: ...banana slicer. Now you're going to hold this very large dish and come over here to the...

Gumbel: Katie, scoop me some ice cream, will you?

Lawrencels: ...dipping cabinet.

Couric: Yeah. What kind?

Gumbel: Use the cookies and cream.

Lawrencels: ...dipping cabinet.

Gumbel: Give me a little bit of everything, all right?

Couric: Cookies and cream?

Roker: Use the cookies and cream.

Couric: Debbie, I think we need scoops that have...

Gumbel: More cookies and cream. Very good.

Couric: ...can hold...

Lawrencels: These are...

Couric: ...more ice...

Lawrencels: ...special scoops. These are...

Gumbel: These are teflon scoops.

Lawrencels: ...these are...

Couric: These are cheap scoops.

Lawrencels: Here. Try this.

Couric: This is like you don't get enough in your scoop scoops.

Lawrencels: No.

Gumbel: OK.

Lawrencels: You're going to do this.

Gumbel: Give me some vanilla.

Lawrencels: You're going to right...

Gumbel: You know...

Lawrencels: ...around the side of the can. That's good.

Couric: What do you want? Vanilla.

Gumbel: Yeah.

Lawrencels: These are special scoops that are teflon-coated.

Couric: Really? My--my forearms got very big...

Gumbel: She's putting her hands on it!

Couric: ...the summer I did this.

Lawrencels: Looks...(unintelligible.)

Couric: I'm sorry. I'm sorry. I'm sorry.

Lawrencels: Now we're going to teach you a little trick here.

Couric: I washed my...

Gumbel: That's good. That's good.

Lawrencels: We are going to teach you a little trick. We want to make a little X-mark...

Couric: Excuse me?

Lawrencels: ...at the top.

Gumbel: How do you do that?

Lawrencels: Make a little X-mark, a little gentle X-mark. And that holds the toppings from falling all the way down. We call it a resting spot for the toppings.

Gumbel: Works...(unintelligible)...

Lawrencels: That's a resting spot. Yeah. Now, you have your choice today of strawberry topping or hot fudge.

Gumbel: Hot fudge.

Roker: Yes. Yes.

Lawrencels: Hot fudge. Do it.

Couric: How about both?

Lawrencels: You can actually put them both. Sure.

Couric: Don't you want to put strawberry on one?

Lawrencels: And you want to push--put it on attractively which you are doing a wonderful job at.

Gumbel: You want me to circle it too or what?

Lawrencels: Oh--oh, just do it.

Roker: Drown it!

Lawrencels: That's great.

Gumbel: Yeah. Yeah.

Couric: Don't most people know how to do...

Lawrencels: That's great!

Gumbel: Obvious. Oh, yeah. It's really worth the...(unintelligible)...

Lawrencels: Now--well, you see how that fudge stayed right on top because of that little X-mark.

Gumbel: Yeah.

Couric: Great.

Lawrencels: Now we're into whipped cream. You have your choice today between vanilla whipped cream or chocolate whipped cream and you want to...

Couric: Choc--do chocolate whipped cream, Bryant.

Gumbel: I don't like chocolate whipped cream.

Couric: I've never seen it before.

Lawrencels: ...shake it. Shake it. Shake it. Shake it. Shake it.

Couric: No? You're not a chocolate fan?

Gumbel: Whoa! Yes!

Lawrencels: And now you are going to turn it all the way upside down. This of course...

Gumbel: Do you want me to take this off?

Lawrencels: ...this plastic thing--OK. No. You're going to leave that there.

Gumbel: Oh. Oh, boy.

Lawrencels: So...

Gumbel: That's right.

Couric: It's a--it's the wrong direction. You're just about to pour it...

Gumbel: Oh, I see. Like this.

Lawrencels: OK. You're going to hold it all the way upside down.

Couric: ...(unintelligible)...by mistake.

Gumbel: Like this?

Lawrencels: That's it. Now, you're going to turn and let some ice cream show because you still want it to look pretty.

Gumbel: All right.

Lawrencels: So you're going to go around in a circular motion. Oh, goodness!

Couric: Wow! That's--whoa!

Lawrencels: That's very good. To practice peaks. Very lovely. You are quite good at whipped cream. OK. Now, you have your choice today between chocolate cookie crunch and roasted almonds.

Gumbel: Al is eating this.

Lawrencels: Always want to...

Gumbel: What do you want?

Roker: The chocolate cookie crunch...

Gumbel: Chocolate cookie crunch.

Roker: I think would be...

Couric: You don't want nuts?

Gumbel: I'm not eating it.

Roker: No. That's OK.

Couric: OK. OK. No. I'm asking Al.

Lawrencels: Oh, lovely. You always have to make it look very attractive. And now for the final touch, we're going to ask you to garnish the strawberry. You always want to pull back this little greenery like a punk rocker. That looks good. Gives it a personality, you see? And now we're going to slice this...

Gumbel: Oh, you have to slice it?

Lawrencels: Yes. We're going to...

Gumbel: X it again?

Lawrencels: We're going to slice it like this. Just a long--about five slices right down.

Gumbel: Oh.

Couric: Like that.

Gumbel: Oh, I see.

Lawrencels: Right down. Five slices. And then we want to just fan it open.

Gumbel: OK. Look, I'm going to--I'm going to take a break right here and then we're going to come back and Al's going to eat this. OK?

Lawrencels: Great.

Gumbel: Don't go away, Debbie.

Lawrencels: Great. Thank you very much.

Gumbel: Hang on just a sec. We're back in just a moment. This is "Today" on NBC.

Lawrencels: Thank you.

Gumbel: Monsieur Albert.

Roker: Thank you. Gimme. Gimme. Gimme. Give me that! Give me that! Give me that!

Al Roker reporting:

Here.

Unidentified Man #1, off camera: Fifteen.

Unidentified Man #2, off camera: Fifteen.

Katherine Couric, co-host:

How much time?

Faith Daniels, anchor:

Want some on your side too?

Roker: Sure.

Man #1 and Man #2: Nine, eight, seven, six, five, four, three...

Daniels: Mmmm. Mmmm. Now that's good.

Man #1 and Man #2: ...two...

Bryant Gumbel, co-host:

Debbie Lawrencels, thank you. I think you made a lot of folks happy here.

Debbie Lawrencels: I'm glad.

Gumbel: You guys...(unintelligible)...for the day.

Daniels: It's OK by us.

Roker: It's a beautiful thing.

Gumbel: That does it for us. Have yourself a good Thursday. See you tomorrow.

Lawrencels: Thank you.

United States
Environmental Protection
Agency

Office of Pesticides
and Toxic Substances
Washington DC 20460

Office of Pesticide Programs

Pesticide Fact Sheet



NAME OF CHEMICAL: Ethyl parathion

REASON FOR ISSUANCE: Settlement Agreement and Voluntary Cancellation
of Most Uses

DATE ISSUED: September, 1991

I. DESCRIPTION OF CHEMICAL

Generic Name: O,O-diethyl-o-p-nitrophenyl phosphorothioate

Common Name: Parathion or Ethyl Parathion

Trade/Other Names: Alkron, Alleron, Aphamite, Bladan, Corothion, Ethyl Parathion, Folidol, E-605, Eosfermo 50, Niran, Orthophos, Panthion, Paramar, Paraphos, Parathene, Parawet, Phoskil, Rhodiatox, Soprathion, Stathion, Thiophos

EPA Shaughnessy Code: 057501

Chemical Abstracts Service (CAS) Number: 56-38-2

Year of Initial Registration: 1948

Pesticide Type: Insecticide

Chemical Family: Organophosphate

U.S. and Foreign Producers:

Cheminova, Denmark: sole manufacturer of technical active ingredient (a.i.) sold in the U.S.; Mobay: technical registration in U.S. but not currently manufacturing; Bayer A.G., Germany.

II. USE PATTERNS AND FORMULATIONS

Application Sites: Vegetable crops, field crops, orchard crops, ornamentals, and mosquito control.

Types of Formulations: Emulsifiable concentrates, granular, dusts, wettable powders

Methods of Application: Airblast, ground boom and aerial application

Application Rates: 0.1 to 10.0 lbs active ingredient per acre

Usual Carriers: Petroleum solvents, clay carriers

III. SCIENCE FINDING

Summary Science Statement

Parathion is a Toxicity Category I organophosphate compound which is extremely toxic as determined in laboratory mammals. Parathion is a potent cholinesterase inhibitor. Acute effects of cholinesterase inhibition can result in severe poisoning requiring hospitalization, or even death. The chemical has also demonstrated adverse chronic effects such as tumors in the adrenal glands, retinal atrophy and degeneration, and degeneration of the sciatic nerve. The Agency has carried out a weight-of-the-evidence analysis and has concluded that parathion is a Group C Carcinogen (possible human carcinogen) and that a quantitative risk assessment for carcinogenicity is not necessary. Parathion was not shown to be teratogenic. Human poisonings from parathion exposure have occurred during mixing/loading, application, early reentry into treated fields, equipment repair and handling, and contact with spray drift. Parathion is very highly toxic to birds and aquatic invertebrates.

1. Chemical Characteristics of the Technical Material

Physical State:	Liquid
Color:	Dark Brown
Odor:	Garlic-like
Molecular weight and formula:	291.26 - $C_{10}H_{14}NO_5$ PS
Boiling point:	157-162 C at 0.6 mm Hg

Vapor Pressure: 3.78×10^{-5} Torr (pure active ingredient)
Solubility in various solvents: Miscible in almost all organic solvents and oils, only slightly soluble in water

2. Toxicological Characteristics

Acute toxicity: Parathion is extremely toxic to mammals by all routes of exposure and is classified in Toxicity Category I (i.e. oral $LD_{50} < 50$ mg/kg). Parathion LD_{50} 's = 1.75 - 15.0 mg/kg.
Major routes of exposure: Dermal and inhalation.
Delayed neurotoxicity: Negative.
Carcinogenicity: This chemical is classified as a Group C (unquantified) carcinogen.
Chronic Effects: Retinal degeneration and sciatic nerve degeneration in life-time feeding studies in the rat.
Cholinesterase inhibition: Chronic dosing, rat: NOEL: 0.5 ppm; LOEL: 5 ppm.
Teratogenicity: Parathion was not teratogenic at levels up to 1.5 and 16 mg/kg in the rat and rabbit, respectively.
Reproduction: Negative.
Mutagenicity: Negative

3. Physiological and Biochemical Characteristics

Mechanism of pesticide action:

This insecticide is active by contact, ingestion, and vapor action. Parathion affects the nervous system by inhibiting the ability of an enzyme called cholinesterase (ChE) to break down acetylcholine which helps transmit signals through the nervous system. This inhibition is only very slowly reversible. When cholinesterase is inhibited, an excess of acetylcholine builds up and impairs the proper functioning of the nervous system. Symptoms of poisoning include headache, dizziness, muscle twitching, tremor, nausea, vomiting, intestinal cramps, diarrhea and general weakness. In more severe cases, parathion poisoning also causes blurred vision, pin-point pupils, tightness in the chest, labored breathing, nervousness, sweating, watering of the eyes, drooling or frothing of mouth and nose, convulsions, coma and even death.

4. Environmental Characteristics

A preliminary review of recently submitted studies indicates that parathion is stable to hydrolysis with half-lives > 30 days at pH 5, 7, and 9. In laboratory conditions it is metabolized in soil under aerobic conditions with a half-life of 56 days. In aerobic aquatic conditions parathion is metabolized rapidly with a half-life of 5.2 days. Under field conditions the rate of parathion dissipation varies, with half-lives of 3 and 32 days reported for studies in cotton fields in California and Missouri, respectively. In the Missouri study parathion was detected once in soil at the 4-8 inch depth; it was not detected deeper than 4 inches in the California study. Parathion dissipated from flood water with half-lives of < 7 days in rice fields in Missouri and California. Neither parathion nor paraoxon was detected in soil samples in aquatic field dissipation studies. Parathion and paraoxon did not accumulate in crops grown in Missouri and California that were irrigated with water from a rice plot treated with six weekly applications of parathion. Parathion has little or no potential to contaminate ground water. This chemical was not included on the list of potential ground water contaminants.

Additional information or new studies are required to complete the Agency's assessment of the environmental fate (degradation, metabolism, mobility, dissipation, and accumulation) of parathion. Studies required to assess spray drift have been submitted and are being reviewed.

5. Ecological Characteristics

A. Avian Effects

1. Oral toxicity: House sparrows and pigeons LD50 = 1.3 mg/kg
2. Dietary toxicity: Mallard and ringnecked pheasant LC50 = 76 to 336 ppm
3. Reproduction: In review.
4. Dermal: Mallard (feet) LD50 = 28.3 mg/kg
Quelea and house sparrow
(under wing joint) LD50 = 1.8 mg/kg

B. Freshwater Aquatic Toxicity

1. Acute Toxicity

(a) Fish:

Mosquito fish	LC50 = 0.04 ppm
Channel fish	LC50 = 2.65 ppm
Fathead minnow	LC50 = 0.5 ppm
Bluegill sunfish	LC50 = 0.4 ppm.

(b) Invertebrates:

Crawfish (<u>Orconectes</u>)	LC50 = 00.04 ppb
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Daphnia magna
Hexagenia
Palaemonetes

LC50 = 00.60 ppb
LC50 = 15.00 ppb
LC50 = 01.50 ppb

(c) Amphibians:

Western chorus frog (Pseudacris triseriata)

LC50 = 1.0 ppm (0.3 - 2.0 ppm)

2. Chronic Effects:

(a) Fish:

Fathead minnow: reproductive impairment: ≥ 4.0 ppb
Bluegill sunfish: morphological malformations: ≥ 0.34 ppb

(b) Invertebrates: Daphnia magna:

MATC = ≥ 0.08 ppb

Gammarus fasciatus:

MATC = < 0.04 ppb

C. Marine and estuarine toxicity:

1. Acute Toxicity

(a) Fish: Sheephead minnow LC50 = 6 ppb
Striped bass LC50 = 17.8 ppb

(b) Invertebrates: Brown shrimp LC50 = 1.0 ppb
Mysid shrimp (Mysidopsis bahia)
LC50 = 120 ng/l (110-140 ng/l)

2. Chronic Toxicity

(a) Invertebrates: Oyster larvae: growth inhibition: EC50 = $> 0.05 < 1.00$ ppm
Oyster: shell deposition: EC50 = 0.85 ppm.

D. Endangered Species:

Previous consultations with the Fish and Wildlife Service have resulted in jeopardy opinions and labeling requests regarding the risks to several endangered species (including birds, bats, fish, crustaceans and aquatic invertebrates) of exposure to various parathion-treated crops including alfalfa, apples, barley, corn, cotton, pears, and wheat) and aquatic sites. Use sites not included in these earlier consultations are now under consideration in consultations initiated in March, 1991. It is anticipated that the results of these interagency consultations will be available in December, 1991.

IV. SUMMARY OF REGULATORY POSITION AND RATIONALE

1. Background

Parathion was first registered for use in the United States in 1948. In 1986, the Agency alerted registrants of its concerns regarding the risks of exposure to parathion for farmworkers during mixing/loading/application of the pesticide, through entry into treated fields and exposure of agricultural workers, and sometimes members of the general public, to spray drift. Registrants were also notified of the Agency's concern about the risk to birds of exposure to parathion. The Registration Standard, issued in 1986, also noted that EPA was considering putting Parathion in Special Review.

Parathion is one of the most toxic chemicals registered with EPA and is a Restricted Use pesticide (not available to the general public). Parathion's ability to rapidly pass through the skin to cause acute poisoning is its major safety hazard. Acute parathion poisoning is produced as a consequence of cholinesterase (ChE) inhibition (see page 3, Mechanism of pesticide action).

Cholinesterase inhibition associated with organophosphates, including parathion, is only slowly reversible, leaving affected individuals at significant risk from subsequent exposure. There is also a growing body of evidence that short term exposure to parathion may have long term neurological, behavioral and perhaps ocular (retinal degeneration) effects.

Parathion is one of the most frequently-cited causes of pesticide deaths and poisonings worldwide. An examination of incident reports, hospitalization data, and mortality data compiled over the last 20 years show parathion is consistently at or near the top of the list of pesticides responsible for serious systemic poisonings (not just skin or eye irritations), hospitalizations, and deaths.

Parathion is also very highly toxic to birds. While there is no systematic system of reporting bird kills, there are many reported incidents of deaths involving several species. Waterfowl, primarily geese, were the predominant group of birds killed. Parathion is also acutely toxic to aquatic invertebrates which may adversely affect fish vitality.

2. Settlement Agreement canceling all parathion use except on 9 field crops

EPA has reached a settlement agreement in principle to limit the use of parathion to nine field crops (alfalfa, barley, corn, canola, cotton, sorghum, soybeans, sunflower, and wheat). Registrants may not sell any product permitting the use on canola until EPA determines that appropriate residue data have been submitted. The registrants have agreed to voluntarily withdraw all other registered uses (over 80) including all use on fruit, nut, and vegetable crops (except sweet corn). The agreement also imposes severe restrictions on the remaining uses. Under the agreement, parathion may only be applied aerially by a certified commercial applicator. No hand harvesting is permitted. Other protective measures include engineering controls (closed mixing/loading systems), protective clothing requirements, spray drift buffer zones, and required reporting to EPA's Office of Compliance Monitoring (202-260-3375) of exposure incidents involving workers, spills, spray drift, or the deaths of birds or other wildlife.

3. Notice of Intent to Cancel (NOIC)

EPA intends to issue a Notice of Intent to Cancel (NOIC) the field uses of parathion in the near future. Although the settlement agreement imposes severe restrictions on the use of parathion on field crops, the Agency remains concerned that these uses still may result in unacceptable risks of exposure to agricultural workers, to the general public through pesticide spray drift, to birds and aquatic invertebrates (part of the food chain for fish). The Agency will also evaluate the risks of exposure to parathion residues in food as a result of parathion use on field crops and on imported food that has been treated with parathion. As required under FIFRA, the Agency will submit its risk/benefit assessment of parathion to the Scientific Advisory Panel (SAP) and to the Secretary of the USDA for comment on the Agency's proposed cancellation action.

4. Tolerances

EPA is currently reassessing the appropriate methodology for determining acute dietary risks (where it may be more appropriate to examine the risk from individual servings of treated crops rather than to average the risk from large numbers of servings). Once these issues are resolved, the Agency will issue a Notice concerning any proposed tolerance reductions or revocations. Since the actions taken on parathion are based on non-dietary concerns, EPA is soliciting public comment on whether parathion tolerances should be revoked (i.e. should EPA allow imports of treated food from countries where the use of parathion is permitted).

5. Existing Stocks

1. Sale. After November 15, 1991 sale by registrants of existing stocks of canceled pesticide products containing parathion (products labelled for uses other than the 8 field crops) is prohibited.

After December 1, 1991 sale by all other persons of these canceled products is prohibited unless the stocks are restickered with the approved label (aerial application only on 8 field uses with additional protective measures) and are in containers which are compatible with the use of the engineering controls required under the terms of the agreement.

In addition, between voluntary cancellation and November 15, 1991, a registrant may not sell any products containing parathion unless the product is stickered to clearly notify any prospective purchaser of the end-sale and end-use dates (see 14 below) and states that a refund of the purchase price will be provided to any individual who is unable to sell or use the product before those dates.

2. Use. Existing stocks of products containing parathion can be used according to the label instructions for any use appearing on the label until December 31, 1991. After December 31, 1991, all use of existing stocks of parathion products other than on the approved field crops in accordance with all of the terms in the settlement agreement, will be prohibited.

3. Disposal. Most of these canceled products are defined as hazardous wastes. You can contact your distributor for correct classification and contact your state or local hazardous waste authority for information regarding safe disposal at a hazardous waste facility in your area. Alternatively, you can contact your distributor to arrange for return and refund of the purchase price by the manufacturer.

4. Export. Once parathion technical or products containing parathion are canceled by EPA they may only be exported to the country of origin (Denmark) and/or those countries which permit parathion imports. EPA will notify foreign governments and the United Nations International Registry of Potentially Toxic Chemicals (IRPTC) of the cancellation of any parathion products. IRPTC is compiling worldwide information on "banned" and "severely restricted" chemicals for the Prior Informed Consent (PIC) list. The PIC list will make it possible to quickly identify countries where parathion products may not be exported.

CONTACT PERSONS AT EPA

Brian Steinwand: 703 308 8174
Kathy Pearce: 703 308 8016

FAX: 703 308 8041

Mailing address:

Brian Steinwand
Special Review Branch (H7508W)
Special Review and
Reregistration Division
Office of Pesticide Programs
Environmental Protection Agency
401 M Street, S. W.
Washington, DC 20460

Office location:

Special Review Branch,
3rd Floor
2800 Jefferson Davis Highway
Arlington, VA

DISCLAIMER: The information presented in this Chemical Information Fact Sheet is for informational purposes only and may not be used to fulfill data requirements for pesticide registration and reregistration.



Pesticide Fact Sheet

Name of Chemical: DIAZINON

Reason for Issuance: REGISTRATION STANDARD

Date Issued: DECEMBER 1988

Fact Sheet Number: 96.1



1. DESCRIPTION OF CHEMICAL

Common Name: Diazinon

Trade and Other Names: Spectracide, D.Z.N., Knox-Out

EPA Shaughnessy Codes: 057801

Chemical Abstracts Service (CAS) Number: 333-41-5

ENT Registry Number: 19507

Year of Initial Registration: 1956

Pesticide Type: Insecticide

Chemical Family: Organophosphate

U.S. and Foreign Producers: Ciba-Geigy, Trans Chemic Industries Inc.,
and Makhteshim Agan (America) Inc.

2. USE PATTERNS AND FORMULATIONS

Application: Aerosols, sprays, pet collars, ear tags, dips, ground
blast, aerial, and soil incorporation.

Annual Usage: 10 million pounds active ingredient (1985 data).

Predominant Use(s): Agricultural, Home and Garden uses.

Types of Formulations: Dusts, emulsifiable concentrates, granules,
impregnated materials, liquids, microencapsulated, pressurized
sprays, soluble concentrates, wettable powders.

3. SCIENCE FINDINGS

Summary Science Statement

Diazinon is not oncogenic in the Fisher F344 rat or in the B6C3F1 mouse. Diazinon does not induce developmental toxicity in rats or rabbits at dose levels up to and including 100 mg/kg/day (highest dose tested).

Based on acceptable laboratory data, technical diazinon is characterized as very highly toxic to waterfowl on an acute oral basis, with an LD₅₀ of 6.38 mg/kg for mallard ducks. Avian dietary studies characterized diazinon as highly toxic to upland game birds with a dietary LC₅₀ of 245 ppm for bobwhite quail. Supplemental data characterize diazinon as very highly toxic to waterfowl with a dietary LC₅₀ of less than 47 ppm for mallard ducks. End-use formulations of diazinon are characterized as very highly toxic to waterfowl, upland game birds and songbirds on acute oral and dietary basis. Technical diazinon and its end-use formulations are characterized as very highly toxic to aquatic organisms. It is considered highly toxic non-target insects.

Diazinon degrades rapidly under aerobic, anaerobic, aquatic anaerobic and sterile soil conditions. Microbial degradation appears to be the major pathway for the degradation of diazinon. The most probable mechanism responsible for degradation under sterile and anaerobic soil conditions appears to be chemical hydrolysis in acidic soils. Supplemental hydrolysis data indicate that diazinon is stable with respect to hydrolysis at pH 7 and 9 but hydrolyzes in non-sterile water with a pH of 5.

The major soil degradate is oxypyrimidine. Oxypyrimidine is more persistent than diazinon under aerobic and sterile, anaerobic and anaerobic aquatic soil conditions.

Diazinon with a 4 day EC50 of 4.14 mg/L and a 7 day EC50 of 3.7 mg/L is characterized as being moderately toxic to freshwater green alga. Diazinon caused greater than 25% detrimental effect in plant vigor in tomatoes, cucumbers, onions, and carrots. Diazinon caused a greater than 25% detrimental effect in seed germination in oats, tomatoes, and carrots. No detrimental effect was seen for seedling emergence.

Chemical Characteristics of the Technical Material

Physical State: Liquid

Color: Amber and brown

Odor: Mild, sweet, and aromatic

Molecular Weight and Formula: (304.3) $C_{12}H_{21}N_2O_3PS$

Boiling Point: 83-84°C at 0.002 mm Hg

Vapor Pressure: 1.4×10^{-4} mm at 20°C

Density: 1.12 g/ml at 20°C

Solubility in various solvents: In petroleum oils, 60 ppm in water at 25°C and 40 ppm in water at 20°C.

Toxicology Characteristics

Acute Oral: LD50 = 618 mg/kg*

Acute Dermal: LD50 > 2000 mg/kg*

Primary Dermal Irritation: Non-irritating*

Primary Eye Irritation: Non-irritating*

Dermal Sensitization: Positive response in 10% of the human volunteers tested*

Acute Inhalation: LC50 = 3.5 mg/L*

Acute Delayed neurotoxicity: Data gap

Subchronic toxicity: Data gap

Oncogenicity: (mouse and rat) Not oncogenic

Chronic Feeding: Data gap

Metabolism: Data gap

Teratogenicity: (Rabbit and Rat) No developmental toxicity at doses up to and including 100 mg/kg/day.

* This information may not be applicable to all currently registered manufacturing use products (MUPs) of diazinon. The Agency is requiring additional toxicity studies to determine the toxicological similarities or dissimilarities of the registered MUPs.

Reproduction: Data gap

Mutagenicity: Data gap

Major routes of exposure

Dermal, oral and inhalation

Physiological and Biochemical Characteristics

Mechanism of Pesticidal Action: Cholinesterase Inhibition

Metabolism and Persistence in Plants and Animals: Data gap

Environmental Characteristics

Diazinon degrades rapidly under aerobic, anaerobic, aquatic anaerobic and sterile soil conditions. The major soil degradate is oxypyrimidine. Oxypyrimidine is more persistent than diazinon under aerobic and sterile, anaerobic and anaerobic aquatic soil conditions. Diazinon's potential to contaminate groundwater is unknown.

Ecological Characteristics

Avian acute toxicity:

3.2 mg/kg (Red-winged blackbird)	-Very highly toxic
6.3 mg/kg (Mallard duck)	-Very highly toxic
10 mg/kg (Bobwhite quail)	-Very highly toxic

Avian dietary toxicity:

< 47 ppm (Mallard duck)	-Highly toxic
245 ppm (Bobwhite quail)	-Highly toxic

Freshwater fish acute toxicity:

Warmwater LC50 = 136 ug/L (Bluegill sunfish)	-Highly toxic
Coldwater LC50 = 90 ug/L (Rainbow Trout)	-Very highly toxic

Marine fish acute toxicity:

LC50 = 1400 ug/L (Sheepshead minnow)-Moderately toxic

Freshwater invertebrate toxicity:

LC50 = 0.2 mg/L (Gammarus fasciatus)-Very highly toxic

Marine invertebrate toxicity: Data gap

Non-Target Insects:

LD50 = 0.22 ug/bee (contact: Honey Bees)	-Highly toxic
LD50 = 0.2 ug/bee (oral: Honey Bees)	-Highly toxic

TOLERANCE ASSESSMENT

Tolerances have been established for residues of diazinon in a variety of raw agricultural commodities, ~~in meat, fat and meat byproducts~~ (40 CFR 180.153), food additives (40 CFR 185.1750) and in food handling establishments (40 CFR 185.1750), and feed handling/processing establishments (40 CFR 186.1750). Tolerances for residues of diazinon are currently expressed as residues of diazinon per se.

Codex MRL's, Canadian, and Mexican tolerances have been established for many of diazinon's registered uses. Compatibility of these tolerances to that of U.S. tolerances cannot be determined until all additional metabolism and residue studies are available.

Based on inhibition of plasma cholinesterase observed in a 90 day rat feeding study a NOEL of 0.009 mg/kg/day was established. A provisional acceptable daily intake (PADI) has been established at 0.00009 mg/kg/day utilizing an uncertainty factor of 100. The PADI is provisional because the existing data base on diazinon is lacking chronic feeding studies, and a multi-generation reproduction study.

4. Required Unique Labeling

- o Restricted use Statement for all commercial outdoor uses (e.g., turf, and agricultural).
- o Restricted use Statement for residential products in toxicity category I or II (danger or warning).
- o Homeowner Protection Statements for indoor and outdoor application.
- o Institutional use Protection Statements for hospitals and schools.
- o Feed and Food Handling Establishments statements.
- o Worker Protection Statements for Toxicity Categories I, II and III end-use formulations.
- o 24-Hour Interim Reentry Interval (commercial and greenhouse use).

5. Summary of Regulatory Positions

o The Agency is deferring a decision at this time on whether to place diazinon into Special Review for its potential hazard to avian species resulting from its use on agricultural crops, on turf and other grassy sites (e.g., athletic fields, recreational parks, home lawns).

o The Agency is classifying all commercial outdoor uses (agricultural crops, ornamentals, and turf) of diazinon for restricted use, based upon its known toxicity to birds and aquatic species.

o All diazinon end-use products that are in Toxicity Category I or II (DANGER or WARNING) and bear product labeling that directly recommends residential use or reasonably can be interpreted to permit residential use are classified for restricted use. Such products may be used only by certified applicators or persons under their direct supervision. In the past, the Agency has allowed these types of products to be labeled, "For Agricultural Use Only" or "For PCO Use Only" in an attempt to limit use to commercial or trained applicators. However, these statements are unenforceable.

o The Agency will be requiring the following testing of a series of typical end use products: acute oral, acute dermal, primary dermal irritation, primary eye irritation, dermal sensitization, and acute inhalation if appropriate. The Agency will reserve alternative product formulations testing, pending submission and review of toxicity testing on the stabilized technical diazinon products (manufacturing use products).

o The U.S. Fish and Wildlife Service, Division of Endangered Species and Habitat Conservation (DESHC) has determined that certain uses of diazinon, including uses on corn and sorghum may jeopardize the continued existence of endangered species. Based on this determination, DESHC specified reasonable and prudent alternatives to avoid jeopardizing the continued existence of the identified species by these uses. EPA is developing a program to reduce or eliminate exposure to these species to a point where use does not result in jeopardy. PR Notices 87-4 and 87-5, which specified labeling requirements designed to reduce or eliminate exposure to endangered species, have been withdrawn. The Agency will issue a notice of any necessary regulatory actions when the program is developed.

o The Agency will require each registrant of a manufacturing use product to submit the following toxicity studies on their current formulations: acute oral, acute dermal, acute inhalation, primary dermal irritation, primary eye irritation, dermal sensitization, and a 6-week rat feeding study. The Agency may require additional toxicity testing based upon its evaluation of these studies.

o The Agency will impose a 24-hour interim reentry interval for all commercial uses of diazinon (greenhouses, agricultural).

o The Agency is revising worker safety and protective equipment statements for end use products containing diazinon.

o The Agency is not imposing a ground water contamination advisory statement for diazinon products at this time. The Agency will assess the potential of diazinon for ground-water contamination after receipt and review of environmental fate data and will determine whether regulatory action is necessary.

o The Agency is imposing additional statements for all end-use products intended for use in and around the home.

o The Agency has determined that diazinon products must bear revised and updated labeling for hazards to nontarget species.

o The Agency will propose tolerance revocation for rutabagas, red chicory tops, and dandelions (40 CFR 180.153).

o Residue data must be submitted and tolerances must be proposed for corn fodder and forage, and either sorghum forage and fodder, or wheat forage, hay and straw, and soybean straw and hay.

o For the following crops; sorghum fodder and forage, soybean straw and hay, and sugarcane forage, the registrant is given the choice of developing and submitting data in support of tolerances, or of adding label restrictions against the feeding and grazing of treated crops to livestock. Each registrant must inform the Agency by 90 days of receipt of this Registration Standard which option he chooses. If he selects the label restrictions, labeling submitted at the 9 month deadline must include the grazing/feeding restrictions.

o The Agency will not grant any significant new tolerances or any significant new food uses for diazinon until the required residue chemistry and toxicology studies have been submitted and reviewed.

o The Agency is not requiring additional residue data to support the established tolerances for diazinon in or on guar beans and coffee beans.

o The Agency will revise commodity definitions for certain raw agricultural commodities listed in 40 CFR 180.153.

a) Tolerance listing "peas with pods (determined on peas after removing any shell present when marketed)" will be revised to read, "peas, succulent".

b) Tolerance listing "bean forage" will be revised to read, "bean vines".

c) the tolerance listing for "wheat forage and straw" was omitted from listing and will read "wheat forage and straw 0.05 ppm".

o The common name "diazinon" will appear before the chemical name on the pesticide label. Labels must be revised to reflect this.

o Petroleum distillates and xylene based solvents must be declared as inert ingredients.

o The Agency has identified certain data that will receive immediate review when submitted;

158.240 Residue Chemistry
 - Plant and Animal Metabolism
 - Special Storage Stability (EUP)

158.290 Environmental Fate
 - Hydrolysis
 - Photolysis

158.340 Toxicology
 - Acute Toxicity Studies (MUP)
 - 6 week Feeding study (MUP)
 - Neurotoxicity study (MUP)
 - Acute Toxicity Studies (TEP)

158.490 Ecological Effects (all)

6. Summary of Major Data Gaps

Timeframe Ranges

Toxicology

12-50 Months

Environmental Fate/Exposure

9-39 Months

Ecological effects

9-30 Months

Residue Chemistry

18-24 Months

Product Chemistry

9-12 Months

7. CONTACT PERSON AT EPA

George LaRocca
Product Manager (15)
Insecticide Rodenticide Branch
Registration Division (TS-767C)
Office of Pesticide Programs
Environmental Protection Agency
401 M Street, S. W.
Washington, D. C. 20460

Office location and telephone number:

Room 204, Crystal Mall #2
1921 Jefferson Davis Highway
Arlington, VA 22202
(703) 557-2400

DISCLAIMER: The information in this Pesticide Fact Sheet is a summary only and is not to be used to satisfy data requirements for pesticide registration and reregistration. The complete Registration Standard for the pesticide may be obtained from the National Technical Information Service. Contact the Product Manager listed above for further information.



Pesticide Fact Sheet



Name of Chemical: FENITROTHION
Reason for Issuance: REGISTRATION STANDARD
Date Issued: July 30, 1987
Fact Sheet Number: 142

1. DESCRIPTION OF CHEMICAL

Generic Name: 0,0-dimethyl 0-(4-nitro-m-tolyl)
(Chemical) phosphorothioate
Common Name: Fenitrothion
Other Chemical
Nomenclature: 0,0-dimethyl 0-(3-methyl-4-nitrophenyl)
phosphorothioate; 0,0-dimethyl 0-(4-nitro-m-
tolyl) phosphorothioate
Trade Names: Bayer 41831; Bayer S-5660; Bayer S-1102A;
AC-47,300; C 47114; Accothion; Cytel; Cyfen;
Folithion; Sumithion; Agrothion; Dicofen;
Fenstan; Metathion E-50; Verthion; Cekutrothion;
Dybar; Fenitox; Novathion; and Nuvanol.
EPA Shaughnessy Code: 105901
Chemical Abstracts Service (CAS) Number: 122-14-5
Year of Initial Registration: 1975
Pesticide Type: Insecticide/Acaricide
Chemical Family: Organophosphate
U.S. and Foreign Producers: Sumitomo Chemical Company (Japan)

2. USE PATTERNS AND FORMULATIONS

Application Sites: Ornamentals (including outdoor, greenhouse,
and nursery); in forests for spruce
budworm and southern pine beetle control;
and in and around non-food domestic,
commercial, institutional and industrial
areas for household pest control.
Formulation Types: 40% wettable powder (for control of
adult anopheline mosquitoes in human
dwellings), 4 (45.5%) and 8 (76.8%)
pound per gallon emulsifiable concentrates
(forestry, ornamental and domestic,
commercial, institutional and industrial
use), and a 93% soluble concentrate/liquid
(forestry use).
Application Methods: Primarily by ground application equipment;
aerial equipment is used for spruce budworm
control.

3. SCIENCE FINDINGS

Summary Science Statement

Fenitrothion is a moderately acutely toxic cholinesterase-inhibiting pesticide. It is in Toxicity Category II for the oral and dermal routes of exposure and Toxicity Category III for the inhalation route of exposure and is mildly irritating to the eyes and skin (Toxicity Category III). It has not been shown to be a dermal sensitizer and does not demonstrate acute delayed neurotoxic effects. Substantial chronic toxicology and residue chemistry data gaps exist, including metabolism, oncogenicity, mutagenicity, teratogenicity, and reproductive effects. Human epidemiological evidence and a dog chronic feeding study have implicated fenitrothion in causing human eye effects, such as retinal degeneration and myopia. Laboratory data show that fenitrothion is potentially highly to very highly toxic to birds, fish, and aquatic invertebrates, including certain endangered species. Preliminary data indicate that groundwater contamination probably is not a potential threat; however the Agency is unable to conduct a full assessment due to data gaps. The Agency is particularly concerned with potential exposure to applicators using ground application techniques to control southern pine beetles; reentry workers in greenhouses and nurseries; and non-target organisms following forestry uses.

Chemical/Physical Characteristics of the Technical Material

Physical State: oily liquid

Color: Yellow-brownish

Molecular weight and formula: 277.2 - $C_9H_{12}NO_5PS$

Boiling Point: 118 °C at 0.01 mm Hg

Melting Point: 0.3 °C

Specific Gravity: 1.32- 1.34

Vapor Pressure: data gap

Solubility in various solvents: data gap

pH: data gap

Stability: data gap

Toxicology Characteristics (Technical Grade)

Acute Oral: Toxicity Category II (800 and 330 mg/kg in male and female rats, respectively)

Acute Dermal: Toxicity Category II (1200 and 890 mg/kg in female and male rats, respectively)

Acute Inhalation: Toxicity Category III (5.0 mg/L in rats)

Primary Dermal Irritation: Toxicity Category III; mild dermal irritation was reported in a rabbit study.

Primary Eye Irritation: Toxicity Category III; mild irritation after a single application of 0.1 mL into unwashed eyes of albino rabbits.

Skin Sensitization: Not a skin sensitizer

Delayed neurotoxicity: Negative in the hen.

Subchronic Oral (rodent) Testing: Data gap for rodent species (for plasma cholinesterase effects)

Oncogenicity: Data gap for the mouse

Chronic Feeding: NOEL for brain and red blood cell cholinesterase in rats is 10 ppm; systemic NOEL for plasma inhibition in the dog is 5 ppm.

Metabolism: Data gap

Teratogenicity: Data gap

Reproduction: Data gap

Mutagenicity: Data gap for point mutation assay in mammalian cells, structural chromosomal aberration, and other genotoxic effects

Major routes of exposure: Inhalation and dermal exposure to occupants of treated dwellings; dermal and respiratory exposure to applicators and reentry workers.

Environmental Characteristics

Data gaps exist for most studies. Preliminary data indicate that fenitrothion degrades fairly rapidly in soil with a half-life of less than a week in non-sterile muck and sandy loam soils. Preliminary data also suggest fenitrothion is intermediately mobile in a variety of soils ranging in texture from sandy loam to clay. The potential for groundwater cannot be assessed until acceptable environmental fate data are received.

Ecological Characteristics (technical grade)

Avian oral toxicity: highly toxic to upland gamebirds and slightly toxic to waterfowl (acute oral toxicity value to bobwhite quails and mallards was determined to be 23.6 mg/kg and 1190, respectively)

Avian dietary toxicity: highly toxic to upland gamebirds and (8 day) and slightly toxic to waterfowl (sub-acute toxicity value of 157 ppm for bobwhite quail and 2482 ppm for mallards.)

Freshwater fish acute toxicity: moderately toxic to both (96 hr. LC₅₀) warmwater and coldwater fish (1.7 ppm for brook trout; 3.8 ppm for bluegill)

Freshwater invertebrate toxicity: very highly toxic to
 (48 hr. or 96 hr. EC₅₀) aquatic invertebrates
 (3 ppb for Gammarus
fasciatus)

Tolerance Reassessment

There are no domestic uses for fenitrothion on food or feed commodities. There is one established U.S. food additive tolerance which covers residues of fenitrothion in wheat gluten imported from Australia arising from the stored wheat grain treatment registered in that country (2 CFR 193.156[9]). The nature of fenitrothion residues in plants is adequately understood. Submitted data indicate that fenitrothion per se (I), desmethyl fenitrothion (IV), and p-nitrocresol (VII) are the major components of the residue. Animal metabolism studies are not available. In the event that future federal registrations for use of fenitrothion on plant commodities used for animal feeds are established, or regulations covering importation of animal products from countries in which fenitrothion is registered for use are established, additional animal metabolism studies may be required. Analytical methodology for determining levels of residues of fenitrothion, fenitrooxon, and p-nitrocresol in plants is adequate for data collection and tolerance enforcement purposes. Storage stability and residue data are required to support the wheat gluten tolerance. A provisional acceptable daily intake (PADI), based on a one-year dog study with a NOEL of 0.125 mg/kg/day and using a 30-fold safety factor is calculated to be 0.004 mg/kg/day. A Theoretical Maximum Residue Contribution (TMRC) for the U.S. population is calculated to be 0.000038 mg/kg/day, which utilizes 0.94 percent of the PADI.

4. Summary of Regulatory Positions and Rationales

- ° Fenitrothion is not being placed into Special Review at this time. Although the Agency is concerned over the potential adverse impact of fenitrothion on birds and aquatic organisms resulting from the forestry use pattern, comprehensive aquatic and terrestrial field studies are needed in order to evaluate the potential risks to birds and aquatic organisms. The Agency is also requiring submission of special acute and subchronic rat studies to provide additional information to confirm the potential for fenitrothion to cause retinal degeneration and changes in corneal shape and structure in the human eye. Pending receipt and evaluation of these data, labeling modifications or other regulatory action may be warranted.

- ° The Agency is classifying the forestry uses of fenitrothion (spruce budworm and southern pine beetle) for restricted-use due to avian and aquatic invertebrate hazards on an interim basis pending receipt and evaluation of the

aquatic and terrestrial field studies.

° Fenitrothion is highly toxic to honeybees, aquatic invertebrates, and avian species. Endangered species label restrictions are required to protect endangered and threatened species in forest areas.

° Special indoor air residue monitoring studies are required to support continued use of the 40% wettable powder formulation in homes to control adult Anopheline mosquitoes.

° No new tolerances or new food uses will be granted until the Agency has received data sufficient to evaluate the dietary exposure of fenitrothion.

° The Agency is imposing an interim 24 hour reentry interval for the greenhouse and nursery ornamental use pending receipt and evaluation of reentry data.

° Protective clothing statements are required for all products containing fenitrothion.

6. SUMMARY OF OUTSTANDING DATA REQUIREMENTS

	<u>Time Frame*</u>	
<u>Toxicology</u>		
Subchronic oral toxicity--rodent species (for plasma cholinesterase effects)	12	Months
21-day dermal--rabbit	9	"
90-day inhalation--rat	15	"
Oncogenicity--mouse	50	"
Teratogenicity--rat and rabbit	15	"
Reproduction--rat	39	"
Mutagenicity	12	"
Metabolism study	12	"
Special tests--acute and subchronic tests in rats for eye effects	24	"
	9	"
<u>Environmental Fate/Exposure</u>		
Hydrolysis study	9	Months
Photodegradation in water, soil and air	9	"
Aerobic soil metabolism study	27	"
Anaerobic aquatic metabolism study	27	"
Lab volatility study	12	"
Leaching and adsorption/desorption	12	"
Soil dissipation study	27	"
Forestry dissipation study	27	"
Fish accumulation study	12	"
Applicator exposure studies	9	"

* based upon receipt of the Standard by the registrant.

Indoor air/surface residue exposure study

12 "

~~Reentry Data~~

27 "

Fish and Wildlife

Avian reproduction

24 Months

Actual field testing--birds and aquatic organisms

48 "

Acute toxicity to freshwater invertebrates--

typical end-use product

9 "

Fish early life stage and aquatic

invertebrate life cycle

15 "

Plant Testing Requirements

Seed germination/seedling emergence

9 Months

Vegetative vigor

9 "

Aquatic plant growth

9 "

Residue Chemistry

Residue analytical methods

18 Months

Storage stability

18 "

Residue data (wheat gluten)

24 "

Product Chemistry

9-15 Months

7. CONTACT PERSON AT EPA

William H. Miller

Product Manager (16)

Insecticide-Rodenticide Branch

Registration Division (TS-767C)

Office of Pesticide Programs

Environmental Protection Agency

401 M Street, S. W.

Washington, D. C. 20460

Office location and telephone number:

Room 211, Crystal Mall #2

1921 Jefferson Davis Highway

Arlington, VA 22202

(703) 557-2400

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540/FS-89-067



Pesticide Fact Sheet

EXHIBIT F

Name of Chemical: COUMAPHOS

Reason for Issuance: REGISTRATION STANDARD

Date Issued: SEP 27 1989

Fact Sheet Number: 207

1. DESCRIPTION OF CHEMICAL

Common Name: Coumaphos

Chemical Family: Organophosphate

Pesticide Type: Insecticide/acaricide

Chemical Name: 0,0-diethyl 0-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) phosphorothioate

Trade Names: Bay 21/199, Asuntol, Muscatox, Resitox, Baymix, Meldane, Co-Ral and Negashunt

Other Chemical

Nomenclature: 0-3-chloro-4-methylcoumarin-7-yl
0,0-diethyl phosphorothioate; 3-chloro-7-diethoxyphosphino-thioxyloxy-4-methylcoumarin; 0-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) 0,0-diethyl phosphorothioate (Chemical Abstracts, 9th Collective Index); 3-chloro-7-hydroxy-4-methylcoumarin 0-ester with 0,0-diethyl phosphorothioate (8th Collective Index); 0,3-chloro-4-methyl-2-oxo-2H-chromen-7-yl 0,0-diethyl phosphorothioate; [0-(3-chloro-4-methyl-7-coumarinyl)] 0,0-diethyl phosphorothioate; 0,0-diethyl 0-(3-chloro-4-methyl-7-coumarinyl) phosphorothioate; phosphorothioic acid 0-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) 0,0-diethyl ester; 3-chloro-4-methylumbelliferone, 0-ester with 0,0-diethyl phosphorothioate; 0,0-diethyl 0-(3-chloro-4-methylumbelliferone thiophosphate

Year of Initial Registration: 1958

CAS Registry Number: 56-72-4

EPA Pesticide Chemical Code (Shaughnessy Number): 036501

U.S. Manufacturer: Bayvet, a division of Cutter Laboratories

USE PATTERNS AND FORMULATIONS

Coumaphos is applied as a direct animal treatment to control arthropod pests of beef cattle, dairy cattle, sheep, goats, horses and swine. ~~It is used to treat swine bedding.~~ Registered control claims are for face flies, horn flies, fly larvae, cattle grubs, ticks (including ear tick), lice, mites, screwworms, sheep keds and fleeceworms. Methods of application consist of dusts, sprays, dips, pour-ons, dust bags and backrubber oilers. Annual usage is 264,000 to 525,600 lbs (1986 estimate). The predominate use is on beef cattle (98%). A relatively small amount is used on dairy cattle (<2%) and swine (<1%).



Current Status and Summary Science Statement

Toxicity data requirements for registration of products containing coumaphos (including acute toxicity testing on end-use product formulations) have been met, except for a 21-day dermal toxicity study, a non-rodent chronic toxicity study, a reproduction study, and a structural chromosome aberration study. Technical coumaphos is highly acutely toxic by the oral and inhalation routes of exposure (Toxicity Category I and II, respectively) and moderately acutely toxic by the dermal route of exposure (Toxicity Category III) based on studies using rats, rabbits and guinea pigs. Technical coumaphos causes only mild eye and dermal irritation (Toxicity Category III and IV, respectively), and is nonsensitizing. End-use product formulations fall in a range of Toxicity Categories from I to III. Coumaphos does not produce organophosphate-type delayed neurotoxicity, based on acute neurotoxicity testing in hens. The oncogenic potential of coumaphos is satisfactorily defined. In vitro microbial studies for gene mutation and DNA damage coumaphos did not cause a mutagenic response, and when tested in the rat and mouse, there were no carcinogenic effects noted. Coumaphos is not a developmental toxicant, or teratogen based on findings in studies utilizing rats and rabbits. Results of a chronic feeding study using rats show that cholinesterase (plasma and erythrocyte) is the primary target of coumaphos. Decreased body weight gain is a secondary effect. In a rat metabolism study, coumaphos was rapidly excreted. There were no dose-related changes in metabolism or evidence of activation/bioaccumulation.

The coumaphos data base for ecological effects testing is complete, with the exception of two special studies. Based on the results of laboratory studies using birds, fish, and aquatic invertebrates, technical coumaphos is moderately acutely toxic to fish and very highly acutely toxic to birds and aquatic invertebrates. Coumaphos is moderately toxic to birds on a subacute (dietary) basis. Aquatic invertebrates may be potentially exposed to hazardous levels of coumaphos resulting from washing-off of the material from the backs of newly treated

cattle which have entered a body of water. Aquatic residue monitoring is required to assess the potential hazards. Due to the potential for avian exposure resulting from birds feeding in cattle lots and on the backs of cattle, Tier I avian field testing is required to assess possible effects to birds resulting from the direct treatment to livestock.

The environmental fate profile for coumaphos is adequately delineated for the registered use pattern, except for a groundwater assessment. Coumaphos is relatively immobile in aged sandy loam soil, based on findings in a column leaching study. There are no immediate concerns for groundwater contamination from non-point source application of coumaphos. However, the potential does exist for localized, point source contamination in animal treatment areas (particularly where animals are dipped), and as a result of associated disposal practices. Due to increased Agency sensitivity in the area of pesticides and groundwater contamination, environmental fate studies are required so that the Agency can assess coumaphos's potential for point source contamination.

Most of the residue chemistry conclusions drawn in the 1981 Standard have been reversed in the current Standard. Residue chemistry data requirements were not imposed in the 1981 Standard. Since issuance of that Standard, the Agency has published residue chemistry guidelines (Pesticide Assessment Guidelines, Subdivision O, 1982, EPA-540/9-82-023) and other Federal Register (FR) Notices which provide a more stringent interpretation of the existing regulations. As a result of these new guidelines, data are now required in the area of animal metabolism, storage stability and method validation. No changes to coumaphos tolerances are indicated at this time.

The Agency is unable to totally assess the safety of current tolerances and establish an acceptable daily intake (ADI) value for coumaphos because of the absence of chronic toxicity studies (reproduction and dog chronic toxicity), and outstanding residue chemistry data. However, a preliminary dietary exposure analysis has been performed for coumaphos. Based on the results of this analysis, current coumaphos tolerances are considered to be adequate to protect the public health. When the remaining data requirements have been fulfilled, the Agency will perform a final reassessment of coumaphos tolerances.

Chemical/Physical Characteristics of the Technical Material

Empirical Formula: $C_{14}H_{16}ClO_5PS$
Molecular Weight: 362.8
Color: grey to tan
Physical state: powder to granules
Odor: characteristic sulfur
Melting Point: 90 to 95 °C

Boiling Point: 20 °C at 10^{-7} mmHg

Solubility: (at 20 °C): g/100 mL at 20 C

acetone	23.82
methylene chloride	6.39
denatured alchohol	0.90
xylene	0.90
hexanes	0.07
water	insoluble at 0.002
octanol	0.13
odorless mineral spirits	0.09
diethyl phthalate	21.50

Vapor Pressure: 1×10^{-7} mmHg

Density, Bulk Density, or

Specific Gravity: granules: 30.06 lb/cu ft, loose; 30.85 lb/cu ft, packed. mhammermilled: 24.35 lb/cu ft, loose; 30.51 lb/cu ft, packed

pH: 7.23 at 1 g/100 mL

Stability: hydrolyses slowly under alkaline conditions; stable under normal storage conditions and use; incompatible with piperonyl butoxide

Storage Stability: Stable (<6% loss) in glass vials up to 8 weeks at -12 to 50 C, dry and at pH 4-10, at 83% moisture, exposed to aluminum, and stainless steel; stable exposed to sunlight for 4 days.

Toxicology Characteristics

Acute Oral: Toxicity Category I (LD_{50} of greater than 240 mg/kg in males rats and 17 mg/kg in female rats)

Acute dermal: Toxicity Category III (LD_{50} of greater than 2400 mg/kg in rabbits)

Acute inhalation: Toxicity Category II (LC_{50} dose for a 1-hour is 341 mg/m³ in female rats and greater than 1080 mg/m³ in male rats)

Primary eye irritation: Toxicity Category III, mild eye irritation reported

Primary dermal irritation: Toxicity Category IV, very minor dermal irritation reported

Skin sensitization: No observable evidence of dermal sensitization

Delayed Neurotoxicity: Did not induce delayed neurotoxicity in an acceptable study in hens.

Subchronic non-rodent/
rodent studies: None available. Not required since chronic data supercede need for subchronic testing.

21-day dermal toxicity: Required Study

Chronic toxicity: Dog study is required. Rat study NOEL is 0.07 mg/kg for decreased cholinesterase activity.

Oncogenicity: The mouse and rat chronic toxicity/ oncogenicity studies did not reveal any evidence that coumaphos is oncogenic.

Mutagenicity: Negative in all areas of mutagenicity tested. A structural chromosomal aberration study is required.

Teratogenicity: Rat teratology study NOEL and LEL were 5 and 25 mg/kg (based on the observation of cholinergic effects), respectively. The developmental NOEL was greater than 25 mg/kg (HDT). Rabbit teratology study maternal NOEL and LEL were 2.0 and 18.0 mg/kg, respectively; developmental NOEL was greater than 18.0 mg/kg (HDT).

Reproduction: Required study

Metabolism: In a rat metabolism study, coumaphos was rapidly excreted. No dose-related changes in metabolism or evidence of activation/bioaccumulation were noted in this study.

Environmental Characteristics

Based on the results of a column leaching study, coumaphos can be characterized as persistent, but immobile in sandy loam soils. There are no immediate concerns for groundwater contamination from non-point source application of coumaphos. However, the potential does exist for localized, non-point source contamination in animal treatment areas (particularly where animals are dipped), and as a result of associated disposal practices. In order to evaluate the potential for point source contamination, special studies are required: a photodegradation study in soil, a photodegradation study in water, an adsorption/desorption study, a hydrolysis study and a retrospective field dissipation study.

Ecological Characteristics

Based on the results of acceptable laboratory data, technical coumaphos is characterized as highly to very highly toxic to birds, moderately toxic to fish and highly toxic to aquatic invertebrates:

- Acute LD₅₀ (mallard): 29.4 mg/kg
- Acute LD₅₀ (pheasant): 7.94 mg/kg
- Dietary LC₅₀:
 - 401 ppm (mallard)
 - 82 ppm (bobwhite)
- Freshwater invertebrates toxicity (96-hr LC₅₀) for amphipods: 0.15 ppb
- Fish acute toxicity (96-hr LC₅₀) for rainbow trout: 5900 ppb
- Fish acute toxicity (96-hr LC₅₀) for bluegill sunfish: 5000 ppb

Results of laboratory testing, in conjunction with theoretical monitoring, indicate that aquatic invertebrates may be potentially exposed to hazardous levels of coumaphos resulting

from washing-off of the material from the backs of newly treated cattle which have entered a body of water, such as a pond or stream. To evaluate the potential risk, a residue monitoring study is required. There is a potential for avian exposure resulting from birds feeding in cattle feedlots and on the backs of cattle. Tier I avian field testing is required to assess possible effects to birds resulting from direct treatment to livestock.

Tolerance Assessment

U.S. tolerances are established for residues of the insecticide coumaphos, O,O-diethyl O-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) phosphorothioate, and its oxygen analog, O,O-diethyl O-3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl-phosphate, in or on raw agricultural products as follows (40 CFR 180.189):

- o 1 ppm in or on meat, fat, and meat byproducts of cattle, goats, hogs, horses, poultry¹, and sheep
- o 0.5 ppm in milk fat (reflecting negligible residues in milk)
- o 0.1 ppm in eggs

Most of the residue chemistry conclusions drawn in the 1981 Standard have been reversed. No residue chemistry data requirements were imposed in the 1981 Standard. Since issuance of that Standard, the Agency has published residue chemistry guidelines (Pesticide Assessment Guidelines, Subdivision O, 1982, EPA-540/9-82-023) and other FR Notices which provide a more stringent interpretation of the existing regulations. As a result of these new guidelines, data are now needed in the area of animal metabolism, storage stability and method validation.

The Provisional Acceptable Daily Intake (PADI) for coumaphos is 0.0007 mg/kg/day and is based on the 2-year rat feeding/oncogenicity study NOEL of 0.07 mg/kg/day (based on plasma cholinesterase inhibition in females) and uncertainty factor of 100. The Anticipated Residue Contribution (ARC) for the United States population is 0.000127 mg/kg/day, occupying 18.2% of the PADI. The two highest calculated exposures for the population subgroups are children 1 to 6 years of age [ARC occupies 33.6% of the PADI] and children 7 to 12 years of age [ARC occupies 25.6% of the PADI]. Based on these calculations, coumaphos applied at the currently registered application rates would not be expected to exceed established tolerances.

The Agency is unable to totally assess the safety of current tolerances and establish an acceptable daily intake (ADI) value for coumaphos because of the absence of chronic toxicity studies (reproduction and dog chronic toxicity), and outstanding data in

¹ There are no longer any federally registered uses for poultry/poultry houses. Therefore, the Agency intends to revoke the tolerances for poultry and eggs.

the area of animal metabolism, method validation and storage stability. When the required data have been submitted and evaluated, the Agency will perform a final reassessment of coumaphos tolerances.

4. SUMMARY OF REGULATORY POSITIONS AND RATIONALES

- The Agency is not initiating a Special Review for coumaphos. No Special Review concerns were identified for this chemical by the Agency during its review of the current data base.

- The Agency is classifying coumaphos 11.6% EC and 42% flowable concentrate end-use products as restricted use due to acute oral hazards.

- The Agency will approve new food/feed tolerances for coumaphos on a case-by-case basis.

- Environmental fate testing is required to evaluate the potential for coumaphos to impact groundwater or surface water resulting from point source application:

- A special aquatic residue monitoring study is required.

- Special Tier I avian field testing is required.

- The Agency will revoke the poultry and egg tolerances, since coumaphos is no longer federally registered for use on poultry or in poultry houses.

- Unique labeling statements are required:

- o Restricted-use classification is required for coumaphos 11.6% EC and 42% flowable concentrate formulations.

- o Special disposal instructions are required for products bearing directions for use a livestock dip treatment.

- o Labels bearing directions for use on goats and sheep must be amended to specify a preslaughter interval (PSI) of 3 days.

- o Product labels must bear revised and updated fish and wildlife statements.

- o Worker safety and protective clothing statements are required for products falling in Toxicity Category I or II.

- o Each end-use product label must be revised to reflect the appropriate signal word and precautionary statements assigned to it based on the results of acceptable acute toxicity testing.

- o Revised labeling must be submitted for those products which do not contain directions for use specifying a maximum single application rate expressed in terms of: (1) amount of

active ingredient per animal; (2) a maximum seasonal application rate or number of applications permitted per season; and (3) a minimum interval between applications, revised labeling must be submitted.

SUMMARY OF OUTSTANDING DATA REQUIREMENTS

Toxicology

21-Day Dermal Toxicity	1 Year
Dog Chronic Toxicity	4 Years
Reproduction Study	4 Years
Chromosome Aberration	1 Year

Environmental Fate/Exposure

Photodegradation in Water and Soil	1 Year
Adsorption/Desorption	2 Years
Special Retrospective Field Dissipation Study	2 "
Hydrolysis Study	1 "
<u>Fish and Wildlife</u>	

Monitoring for Aquatic Invertebrate Mortality and Residues in Water	3 Years
Tier I avian field testing	3 Years

Residue Chemistry

Metabolism data - Animals	1 Years
Residue Analytical Methods	1 "
Storage Stability Data	1 "

Product Chemistry

Remaining Data Gaps	1 -2 Years
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6. Contact Person at EPA

George LaRocca.
Product Manager (15)
Insecticide-Rodenticide Branch
Registration Division (H7505C)
Environmental Protection Agency
Washington, DC 20460
Tel. No. (703) 557-24006

DISCLAIMER: The information presented in this Chemical Information Fact Sheet is for informational purposes only and may not be used to fulfill data requirements for pesticide registration and reregistration.



Pesticide Fact Sheet

EXHIBIT G

Name of Chemical: Acephate
Reason for Issuance: Issuance of a Registration Standard
Date Issued: 10/87
Fact Sheet Number: 140

1. Description of Chemical

Generic Name: O,S-dimethyl acetylphosphoramidothioate
Common Name: Acephate
Trade Name: Orthene
EPA Shaughnessy Code: 103301
Chemical Abstracts Service (CAS) Number: 30560-19-1
Year of Initial Registration: 1974
Pesticide Type: Insecticide
Chemical Family: Organophosphate
U.S. and Foreign Producers: Chevron Chemical Co. (U.S.A.)



2. Use Patterns and Formulations

Application Sites: Agricultural crops; ornamentals (field grown, greenhouse, and home garden); lawns and turf; pasture and rangeland; forestry; indoor homeowner use on houseplants; and commercial applicator use in residential and commercial buildings including food processing establishments.

Types and Methods of Application: Aerial; ground; direct injection into tree trunks; dip treatment (ornamentals); soil incorporated; and sprinklers.

Type of Formulations: Granular, pressurized liquid, soluble concentrates (both liquids and solids), and cartridge.

3. Science Findings

Summary Science Statement: Acephate has a relatively low acute toxicity to laboratory animals through the oral, dermal, and inhalation routes of exposure. Based on the available evidence, i.e., findings from the mouse oncogenicity study, and the mutagenicity assays, the Agency has classified the chemical as a category C carcinogen (a possible human carcinogen). The mouse oncogenicity study indicated a statistically significant increase in the proportion of liver adenomas/carcinomas and hyperplastic nodules occurred only in the high dose (1000 ppm) females and only at the time of terminal sacrifice. The EPA Guidelines for carcinogenic

risk assessment (FR September 24, 1986) were followed for the evaluation and the classification of the oncogenic effect of acephate. Following the guidance set forth in the EPA guidelines, the mouse oncogenic response was considered as "limited evidence."

The available data are not sufficient to enable the Agency to accurately assess the potential risk to humans from this oncogenic effect resulting from exposure to acephate. The data gaps include residue reduction studies, exposure studies, usage data, a dermal penetration study, a glove permeability study, and reentry data.

The available rat reproduction study showed reproductive effects at 50.0 ppm, the lowest dose tested. A new rat reproduction study is needed to determine the no-observable-effect level (NOEL) for these effects and to enable the Agency to assess the potential risk to humans resulting from exposure to acephate.

Methylthioacetate (MTA) occurs as an impurity in the current registered technical material. The available data suggest that the MTA, despite its generally low acute toxicity, may pose a hazard to the optic tract and pituitary gland in rabbits and other mammals at low doses. Data were not provided to demonstrate a NOEL for lesions at these target organs. Since visual impairment is inherently difficult to diagnose in animals, it is possible that this effect occurred in other studies but was not detected. In addition, a mutagenic effect was seen in the mouse lymphoma assay in the activated system. Due to the insufficiency of the submitted data to explain the toxic and mutagenic potential of MTA, the Agency requires that additional studies be performed.

Methamidophos, the cholinesterase-inhibiting metabolite of acephate, is also an insecticide in its own right, and as such, was assessed under a separate Registration Standard issued for the chemical in September 1982. Several of the data gaps identified in that standard have been fulfilled. It is highly toxic by both the oral and dermal routes (Toxicity Category I). Results of two oncogenicity studies show that methamidophos was not oncogenic in rats at dose levels of 2,6,18 and 54 ppm nor in mice at dose levels of 1,5, and 25 ppm. The available teratogenicity studies show that it is not teratogenic to rats or rabbits. The chemical was negative for acute delayed neurotoxicity in the submitted study on hens. The lowest effect level (LEL) for cholinesterase inhibition activity was determined to be 2 ppm (0.05 mg/kg/day) in both the 1-year dog study and the 2-year rat study.

Data gaps for methamidophos include a rat reproduction study and mutagenicity studies.

Chemical Characteristics

Physical State: Solid
Color: White
Odor: Strong, pungent, mercaptan-type
Boiling Point: N/A

Melting Point: 82-89 °C (97% technical)

Flammability: N/A

Solubility in Water: High solubility (65%)

Toxicology Characteristics:

ACEPHATE:

- o Acute Oral - Rat: 945 mg/kg (male); 866 mg/kg (female)
Toxicity Category III
- o Acute Dermal - Rabbit: > 10,000 mg/kg (male)
Toxicity Category III
- o Acute Inhalation - Rat: > 61.7 mg/kg (male and female)
Toxicity Category IV
- o Acute Delayed Neurotoxicity - Hen: Negative at 785 mg/kg of
body weight
- o Mouse Oncogenicity: Female mice fed 1000 ppm of technical
acephate (highest dose tested) had a statistically
significant higher incidence of hepatocellular carcinomas
(15.8%) and hyperplastic nodules (19.7%) than did the
controls.
- o Rat Oncogenicity: Not oncogenic to male and female rats
under the conditions of the study; highest dose tested
was 700 ppm (35 mg/kg).
- o Rat Chronic Feeding: LEL = 5 ppm (0.25 mg/kg) based on the
inhibition of cholinesterase activity in plasma, RBC,
and brain.
- o Dog Chronic Feeding: NOEL = 30 ppm (0.75 mg/kg) based on
the inhibition of plasma, RBC, and brain cholinesterase
activity. NOEL = > 100 ppm (2.5 mg/kg) for systemic
toxicity.
- o Rabbit Teratogenicity: Not fetotoxic or teratogenic at
10 mg/kg (highest dose tested).
- o Rat Teratogenicity: Not teratogenic at 200 mg/kg (highest
dose tested).
- o Mutagenicity: The available studies indicate that acephate
can induce gene mutations, DNA repair, and sister
chromatid exchanges. However, in vivo studies did not
indicate that these effects and structural chromosome
aberrations are produced at a detectable level in an
intact mammalian system.

- o Rat Reproduction: Various reproductive effects (low pregnancy rate, high loss of total litters, high fetal losses, decreased size and weight of total litters, and decreased number of live fetuses) were observed at the lowest dose level tested, which was 50.0 ppm of technical acephate (93% acephate).

METHYLTHIOACETATE (MTA):

- o Acute Dermal - Rabbit: 1720-2820 mg/kg; Toxicity Category II-III. Clinical signs included irreversible absence/diminution of pupillary light reflex and apparent blindness.
- o Acute Inhalation - Rat: 3.47 mg/L; Toxicity Category III.
- o Skin Irritation - Rabbit: 2.6 Primary Irritation Score; Toxicity Category III.
- o Skin Sensitization - Guinea Pig: Nonsensitizing and nonirritating; dose level tested was 0.3 ml (0.3 g).
- o Eye Irritation - Rabbit: Toxicity Category III; dose level tested was 0.1 mL of 93.5% MTA.
- o Mutagenicity - Mouse Lymphoma Assay: Mutagenic to lymphoma cells in the activated system but not in the nonactivated system; levels tested were 1-10,000 ug/ml (activated) and 10-5000 ug/ml (nonactivated).

Physiological and Biochemical Behavioral Characteristics:

Translocation: The available plant metabolism studies show that acephate residues are readily absorbed by the roots and translocated throughout the plant. However, data show that acephate does not accumulate in carrot plants rotated in acephate-treated soil or in fish, daphnia, or diatoms.

Mechanism of Pesticidal Action: Acephate is a contact and systemic insecticide. As an organophosphate, acephate exerts its toxic action by inhibiting certain important enzymes of the nervous system (cholinesterase).

Metabolism and Persistence in Plants and Animals: The metabolism of acephate in plants and animals is adequately understood. Available data show that the residues in or on plants resulting from acephate use may be largely or wholly intact acephate and its metabolite, methamidophos. Available animal metabolism data show that most of the radiolabeled material is rapidly eliminated from the body and that a majority of the material is excreted in the urine.

Methamidophos is not the major metabolite in ruminants. About 80 percent of the radiolabeled material in the urine was associated with unchanged acephate and less than 10 percent with the metabolite O,S-dimethylphosphorothioate. Most of the methamidophos formed is probably eliminated and excreted in the urine as O,S-dimethylphosphorothioate.

Environmental Characteristics:

Due to its rapid leaching behavior, acephate has the potential for ground water contamination. Available data are insufficient to fully assess this potential. Pertinent data (mobility, photodegradation, metabolism, and dissipation) are being required under the Acephate Registration Standard on an accelerated basis.

Available soil metabolism studies show that acephate dissipates rapidly with half-lives of < 3 and 6 days in aerobic and anaerobic soils, respectively. The major metabolite was CO₂ in both types of soil. The available leaching data include a soil thin-layer chromatography (TLC) study and a soil column study. Results of these studies indicate that acephate is mobile in most soils but that aged acephate residues (excluding acephate and its degradate methamidophos) are immobile in sandy loam soil. Apparently most of the applied acephate and the degradate methamidophos degrade to immobile compounds in 20 days.

Ecological Characteristics:

- o Avian Oral Acute Toxicity: 350 mg/kg (mallard) and 140 mg/kg (pheasant)
- o Avian Dietary Toxicity: > 5000 ppm (mallard) and 1280 ppm (bobwhite)
- o Fish Acute Toxicity: > 1000 ppm (rainbow trout) and > 1000 ppm (bluegill sunfish)
- o Freshwater Invertebrate Acute Toxicity: > 1000 ppm (Chironomus) and > 100 (Gammarus)
- o Avian Reproduction: NOEL = > 5 ppm but < 20 ppm for mallard and NOEL = > 20 ppm but < 80 ppm for bobwhite.
- o Honey Bee Acute Toxicity: 1.2 ug/bee.

Based on these studies, acephate is moderately toxic to avian species, practically nontoxic to freshwater fish and freshwater invertebrates, and highly toxic to honey bees.

However, acephate's metabolite, methamidophos, has been shown to be very toxic to birds. Therefore, additional testing (residue monitoring studies) are being requested to complete a hazard assessment for the multiple-application, high-use rate field crops. Appropriate labeling for the protection of endangered species determined to be in jeopardy from use of acephate on forests, range and pastureland, soybeans, and cotton have been developed by the Agency and were imposed under PR Notices 87-4 and 87-5.

Tolerance Assessment:

Refer to Attachment A for the list of currently established tolerances for acephate as well as the tolerance changes to be initiated by the Agency.

To achieve compatibility with the maximum residue levels of the Codex Alimentarius Commission, the following revisions in 40 CFR 180.108, 21 CFR 561.20, 40 CFR 180.315, 21 CFR 561.277, and 21 CFR 193.10 are to be initiated by the Agency.

o 40 CFR 180.108 and 21 CFR 561.20

The acephate tolerances currently established under these sections are to be expressed in terms of only acephate per se, with references to 40 CFR 180.315 and 21 CFR 561.277 indicating that tolerance for the metabolite methamidophos are also in effect.

o 40 CFR 180.315 and 21 CFR 561.277

The methamidophos tolerances currently established under these sections are to be divided into parts (a) and (b) where (a) includes (1) tolerances reflecting uses of methamidophos and (2) tolerances where both acephate and methamidophos formulations are used on the same crop and (b) includes tolerances reflecting uses of acephate formulations alone, i.e., residues of methamidophos resulting from the metabolism of acephate.

o 21 CFR 193.10

These food additive tolerances reflecting crack and crevice treatment in food-handling facilities are to be expressed in terms of only acephate per se, i.e., based on the available data. No residues of the metabolite methamidophos are expected to occur (< 0.001 ppm) in or on these foods.

Also, such a change in the residue definition would require deletion of the paragraph (d)(8) of 40 CFR 180.3, which states that methamidophos residues may not exceed the higher of the two tolerances established for the use of acephate or methamidophos as a pesticide.

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The tolerance for acephate residues in milk has been found likely to be exceeded if maximum levels of spent mint hay or grass hay are included in the dairy animal diet. Labeling restrictions prohibiting the feeding of spent mint hay and grass hay to dairy animals are being imposed under this Standard for the use of acephate on pasture, rangeland, peppermint, and spearmint. If the registrant elects to submit additional residue data to support a lower tolerance for grass and grass hay, or to support a longer pregrazing or preharvest interval for dairy animals, the labeling restriction for use on pasture and rangeland would be imposed as an interim precautionary measure pending submittal and evaluation of these data.

Available data are not sufficient to conduct a full tolerance assessment. Data gaps exist for magnitude of residue studies, residue storage stability studies, a dairy cattle feeding study, a rat reproduction study, and a rat feeding study.

4. Summary of Regulatory Position And Required Unique Labeling

Registration of current registered uses of acephate is to be continued. Additional data to allow the Agency to better define the dietary, occupational, and domestic exposure risks from the registered uses of the chemical are being required. Once the Agency has evaluated these data, it will determine whether the chemical should be placed in Special Review or returned to the normal registration process. Pending submittal and evaluation of these data, no additional tolerances, including temporary tolerances, will be established for acephate and no new uses will be registered, i.e., uses that would result in an increase in the current exposure to humans or in new exposure to humans.

As interim measures to reduce exposure pending submittal and evaluation of the additional studies specified above, the following restrictions are being imposed or, in the case of the last restriction concerning domestic use, continued: A reentry interval of 24 hours for fieldworkers; the use of protective clothing, including chemical-resistant gloves, long-sleeved shirts and long-legged trousers, shoes and socks by mixer/loaders, applicators, and early reentry workers who may be exposed to treated plant surfaces within 24 hours of acephate application; dairy animal feeding restrictions as described above under Tolerance Assessment; and, for domestic use, the restriction not to allow children or pets on treated surfaces until sprays have dried.

The 24-hour reentry interval is being imposed for the use of acephate on agricultural crops, commercially grown ornamentals, in commercial or governmental forestry seed production, and in greenhouses.

As described above under Ecological Characteristics, the Agency has imposed labeling restrictions for the protection of endangered species determined to be in jeopardy from use of acephate.

5. Summary of Major Data Gaps

<u>Toxicology</u>	<u>Date Due</u>
- Acephate	
Rat Reproduction	39 Months
21-Day Inhalation	6 Months (Protocol)
Rat Feeding Study	6 Months (Protocol)
- Methylthioacetate (MTA)	
Acute Oral (Rat and Rabbit)	9 Months
Acute Dermal (Final Report - Rabbit)	9 Months
Acute Inhalation	9 Months
90-Day Dermal (Rabbit)	15 Months
Mutagenicity	12 Months
<u>Environmental Safety</u>	
Avian Residue Monitoring	6 Months (Protocol)
<u>Environmental Fate</u>	
Soil Photodegradation	9 Months
Anaerobic Aquatic Metabolism	27 Months
Adsorption/Desorption	12 Months
Soil Dissipation - Field	27 Months
Irrigated Crop	39 Months
Confined Rotational Crop	39 Months
Spray Drift	6 Months
<u>Exposure</u>	
Applicator (Outdoor and Indoor)	6 Months (Protocol)
Indoor Inhabitants	6 Months (Protocol)
Glove Permeability	6 Months (Protocol)
<u>Residue Chemistry</u>	
Storage Stability	24 Months
Magnitude of Residues	24 Months
Dairy Cattle Feeding	18 Months
Tobacco Residue	24 Months

Benefits

Usage

6 Months

Use-Related Exposure

6 Months

6. Contact Person at EPA

William H. Miller (PM 16)
Insecticide-Rodenticide Branch (TS-767C)
401 M Street SW.
Washington, DC 20460.

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Pesticide Fact Sheet

EXHIBIT H

Name of Chemical: MALATHION
Reason for Issuance: REGISTRATION STANDARD
Date Issued: JAN - 1 1988
Fact Sheet Number: 152



1. DESCRIPTION OF CHEMICAL

Generic Name: O,O-dimethyl phosphorodithioate of diethyl mercaptosuccinate
(Chemical)

Common Name: Malathion

Trade and
Other Names:

S-1,2-bis(ethoxycarbonyl)ethyl O,O-dimethyl phosphorodithioate; diethyl(dimethoxyphosphinothioyl)thiobutanedioate; diethyl mercaptosuccinate S-ester with O,O-dimethyl phosphorodithioate; O,O-dimethyl dithiophosphate of diethyl mercaptosuccinate; [S-(1,2-dicarbethoxyethyl) O,O-dimethyl phosphorodithioate; diethyl mercaptosuccinic acid, S-ester with O,O-dimethyl phosphorodithioate; American Cyanamid Co. (USP 2578,652) Code No. EI4049; Calmathion; Celethion; Cythion (deodorized grade); Chemathion; Malaspray; Detmol MA 96% (Albert & Co., Germany); Emmatos; Emmatos Extra; For-Mal (Forshaw Chemicals); Pyfanon; Hilthion; Karbofos; Kop-Thion; Kypfos; Malamar; Malaphele; Malathion ULV Concentrate; Malatol; Maltox (All-India Medical); Prentox Malathion 95% Spray; Sumitox; Vegfru Malatox; Zithiol; Malmed.

EPA Pesticide Chemical Code (Shaughnessy Number): 057701

Chemical Abstract Service (CAS) Number: 121-75-5

Year of Initial Registration: 1956

Pesticide Type: Insecticide and Miticide

Chemical Family: Organophosphate

U.S. and Foreign Producers: American Cyanamid Company, A/S Cheminova, McLaughlin Gormley King Company, Prentiss Drug and Chemical Corp., Inc., Carmel Chemical Corp., Amvac Chemical Corp., Prochimie International Inc., Gowan Co., Wesley Industries Inc., Trans Chemic Industries Inc., Southern Mill Creek Products Co., Inc., Octagon Process Inc., FMC Corp., and Aceto Chemical Co. Inc.

2. USE PATTERNS AND FORMULATIONS

Application Sites: Terrestrial food crop use on alfalfa, almond, anise, apple, apricot, asparagus, avocado, barley, beets, beets (seed crop), bermudagrass, blackberry, blueberry, boysenberry, broccoli, brussels sprouts, cabbage, cantaloupe, carrot, casaba melons, cauliflower, celery, cherry, chestnut, citrus fruits (nursery stock), clover, collards, corn cotton, cowpeas (hay), crenshaw melons, cucumber, currant, dandelion, date, dewberry, eggplant, endive, fig, filbert, flax, garlic, gooseberry, grapefruit, grapes, grass, grass hay, green beans, guava, honeydew melons, honey ball melons, horseradish, kale, kidney beans, kohlrabi, kumquat, leek, lemon, lespedeza, lettuce, lima beans, lime, loganberry, lupine, macadamia nut, mango, muskmelons, mustard greens, navy beans, nectarine, oats, okra, onion, onion (green), onion (seed crop), papaya, parsley, parsnip, passion fruit, pasture grasses, peach, peanuts, pear, peas, pecan, peppermint, peppers, persian melons, pineapple, rangeland grasses, raspberry, rutabaga, rye, safflower, salsify, shallot, snap beans, sorghum, soybeans, spearmint, spinach, squash, strawberry, sugar beets, sweet potato, swiss chard, tangelo, tangerine, tomato, turnips, vetch, walnut, watercress, watermelons, wax beans, and wheat;

Terrestrial non-food crop use on tobacco, tobacco (transplant beds), ornamental flowering plants, ornamental lawns and turf, ornamental nursery stock, ornamental woody plants, pine seed orchards and uncultivated non-agricultural areas;

Greenhouse food crop use on asparagus, beans, beets, celery, cole crops (including broccoli, cabbage, kale mustard greens, and turnips), corn cucumber, eggplant, endive, lettuce, melons, mushrooms, onion, peas, peppers, potato, radish, spinach, squash, summer squash, tomato, and watercress;

Greenhouse non-food crop use on ornamental plants and Epcot display crops;

Aquatic food crop uses on cranberry and rice;

Aquatic non-food uses on intermittently flooded areas, irrigation systems, and sewage systems;

Forestry uses on forest trees (including Douglas fir, eastern pine, hemlock larch, pines, red pine, spruce, and true fir);

Indoor uses on stored commodity treatment for almonds, barley, field corn, field or garden seeds, grapes (raisin), oats, peanuts, rice rye, sorghum, sunflower, wheat, bagged citrus pulp, and cattle feed concentrate blocks (non-medicated); pet and domestic animal uses for beef cattle, cats, chickens, dairy cattle (lactating and non-lactating), dogs, ducks, geese, goats, hogs, horses (including ponies), pigeons, sheep, and turkeys; animal premise uses for dairy and livestock barns, stables and pens, feed rooms, poultry houses, manure piles, garbage cans, garbage dumps, kennels, rabbits on wire, beef cattle feed lots and holding pens, cat sleeping quarters, dog sleeping quarters, poultry houses; agricultural premise uses for cull fruit and vegetable dumps; household uses for indoor domestic dwellings, human clothing (woolens and other fabrics), mattresses; and commercial and industrial uses for bagged flour, cereal processing plants, edible and inedible commercial establishments, dry milk processing plants, edible and inedible eating establishments, edible and inedible food processing plants, packaged cereals, pet foods and feed stuff.

Methods of Application: Sprays, aerosols and fogging equipment, ground and aerial equipment (including ULV), baits, paints, pet collars, dips, soil, bark and foliar application, dormant and delayed dormant application, animal dust bags and oilers, and cattle feed concentrate blocks.

Formulations: Wettable powders, dusts, granules, emulsifiable concentrates, liquids, solids, impregnated materials, and pressurized sprays, pellets/tablets, liquids (ready to use).

3. SCIENCE FINDINGS

Summary Science Statement

Technical malathion is a mildly acutely toxic pesticide, which is placed in Toxicity Category III based on the oral, dermal and inhalation routes of exposure. Technical malathion is non-sensitizing and only mildly irritating to the eyes and skin (Toxicity Category III and IV, respectively). Additional data are required to assess the neurotoxic potential of malathion. Malathion is a cholinest ras inhibitor, r ducing plasma and red blood cell cholin st ras .

Although the Agency possesses a number of studies on the chronic effects of malathion and its principal metabolite malaoxon, several of these studies are deficient scientifically, and must be repeated.

Of five studies concerning the oncogenicity of malathion and its metabolite, three are acceptable, and demonstrate that malathion is not carcinogenic in two species of rats, and that its metabolite malaoxon is not carcinogenic in mice. Because of questionable liver findings in the malathion mouse study and the malaoxon rat study, new studies must be conducted in these species.

An acceptable rabbit teratology study demonstrated no teratogenicity at dosages up to 100 mg/kg/day. However, developmental and maternal toxicity were noted at dosages of 50 mg/kg/day. A similar study in rats was unacceptable and must be repeated. A 3-generation reproduction study was also unacceptable.

Laboratory data show that technical malathion is potentially highly toxic to aquatic invertebrates, bees, and aquatic life stages of amphibians; moderately toxic to birds, and slightly toxic to fish. Based on theoretical calculations, both terrestrial and aquatic uses of malathion may pose significant risk to aquatic fauna. Reported fish kills and results of field studies suggest that adverse effects to both aquatic and terrestrial fauna may result from normal use of malathion. However, these studies are not adequately documented to enable EPA to propose restrictions on the use of malathion. EPA will reassess the impacts of malathion use on nontarget organisms after the required environmental fate and ecological effects data have been received and reviewed.

The Agency is unable to assess the potential for malathion to contaminate groundwater because the environmental fate of malathion is largely uncharacterized. Preliminary data indicate that malathion is very mobile in loamy sand and loam soils. Additional data are needed in order for the Agency to assess its fate in the environment and potential for contaminating groundwater.

A tolerance reassessment of malathion is not possible at this time, since most of the tolerances are not adequately supported, and because there are gaps in the chronic toxicology data base (chronic feeding studies, teratology study, reproduction study, mutagenicity studies, and a metabolism study). The Theoretical Maximal Residue Contribution (TMRC) for the U.S. population average is 0.1014 mg/kg/day and the Provisional Acceptable Daily Intake (PADI) is 0.02 mg/kg/day based on a human study in which plasma and red blood cell cholinesterase were monitored and a 10-fold uncertainty factor was used. The TMRC occupies 507% of the PADI.

Chemical/Physical Characteristics of the Technical Material

Chemical/Physical Characteristics (technical grade)	Color: colorless, yellow, amber, or brown
	Physical state: Liquid
	Odor: Mercaptan-like
	Specific gravity: 1.2315 at 25°C
	Boiling point: 156-157°C at 0.7 mm Hg
	Solubility: 145 ppm in water at 25°C; completely soluble in most alcohols, esters, high aromatic solvents, and ketones; poor solubility in aliphatic hydrocarbons.
	Vapor pressure: 0.00004 mm Hg at 30°C
	Miscibility: miscible with most organic solvents
	Stability: may gel in contact with iron, terreplate or tinplate

Toxicology Characteristics

Acute Oral: Toxicity Category III (ranges from 1546 to 1945 mg/kg in female rats and 1522 to 1650 mg/kg in male rats).

Acute Dermal: Toxicity Category III (>2000 mg/kg in female and male rats and rabbits).

Acute Inhalation: Toxicity Category III based on toxicity values ranging from 1.7 to >4.0 mg/m³ in rats.

Primary Dermal Irritation: Toxicity Category IV based on mild dermal irritation reported in a rabbit study

Primary Eye Irritation: Toxicity Category III based on findings of mild conjunctival reactions 72 hours post application in rabbits' eyes.

Skin Sensitization: Non-sensitizing

Delayed Neurotoxicity: Data gap.

Subchronic Inhalation: Data gap.

Oncogenicity: Data gaps for mouse (using malathion) and rat (using malaoxon).

Chronic Feeding: Data gaps for rodent and nonrodent (using malathion) and rodent (using malaoxon).

Metabolism: Data gap.

Teratogenicity: Data gap for rat. Data in rabbit indicated a NOEL = 25 mg/kg for developmental effects; it was not teratogenic in any dose group (Highest Dose Tested was 100 mg/kg).

Reproduction: Data gap.

Mutagenicity: Data gap.

Environmental Characteristics

Data gaps exist for environmental fate. Data reviewed by the Agency indicate that malathion is very mobile in loamy sand and loam soils. Adsorption ratios reported (amount adsorbed/initial concentration) were 0.73 to 0.95. Data are needed before the Agency can assess the potential for malathion to contaminate groundwater.

Ecological Characteristics (technical grade)

Avian oral toxicity (8-day LD ₅₀)	167 ppm for ring-necked pheasant and 1485 ppm for mallard.
Avian dietary toxicity (8-day LC ₅₀)	Acute toxicity value of 3497 ppm for bobwhite and >5000 ppm for mallard
Freshwater fish acute toxicity (96-hr LC ₅₀)	200 ppm for rainbow trout and 40 to 103 ppm for bluegill
Freshwater invertebrate toxicity (48-hr EC ₅₀)	1 ppm for <u>Daphnia magna</u>
Estuarine invertebrate toxicity	>1000 ppm for Eastern oyster

Tolerance Assessment

The available data pertaining to metabolism of malathion in plants are inadequate. Additional data are required on the uptake, distribution, and metabolism of malathion in alfalfa, cotton, soybeans, and either wheat or rice. The data pertaining to metabolism of malathion in animals are inadequate. Additional metabolism studies are required that utilize ruminants and poultry. Metabolism studies using cattle, poultry, and swine reflecting direct animal treatment are also required.

Analytical methodology for determining the levels of residues of malathion in plants and animals is adequate. Malathion is detected by the FDA-USDA multiresidue protocols.

Storage stability data demonstrate that residues of malathion in or on frozen plant commodities are stable up to 185 days after application and in milk stored at -10°C for 98 days after application. No data are currently available for animal tissues and are required. Additional storage stability data are also required in order to evaluate the adequacy of the malathion tolerances.

Insufficient data are available on the magnitude and levels of residues of malathion in or on all commodities listed in 40 CFR 180.111 except flax seed, hops, wild rice, and non-medicated cattle feed concentrate blocks. Processing studies are required.

Tolerances must be proposed and appropriate supporting residue data submitted for the following feed items: beanvines and hay; lentil forage and hay; cowpea seed; soybean straw; barley forage, hay and straw; corn forage and fodder; oat forage, hay and straw; rice straw; rye forage and straw; straw of wild rice; sorghum fodder; lespedeza forage; lupine forage; cotton forage; mint hay; peanut hulls, hay and vines; and pineapple forage.

Feed additive tolerances are required for residues of malathion in or on dried hops and spent hops. A tolerance for residues of malathion in or on anise must be proposed together with supporting residue data. Data are needed to support the use of malathion in food handling establishments. In addition, data reflecting the use of malathion on stored, unfinished tobacco are required.

Based on a study in humans in which red blood cell and plasma cholinesterase activity were inhibited at a dose of 0.34 mg/kg (the lowest effect level or LEL), a NOEL has been extrapolated to 0.2 mg/kg/day. A provisional acceptable daily intake (PADI) of 0.02 mg/kg/day has been calculated using a 10-fold uncertainty factor. The PADI is provisional because the existing data base on malathion is lacking chronic toxicity studies, an acceptable teratology study in rats, an acceptable reproduction study, mutagenicity studies, and a metabolism study.

The Theoretical Maximal Residue Contribution (TMRC) for the U.S. population average is 0.1014 mg/kg/day, occupying 507% of the PADI. For children 1 to 6 years of age, the TMRC occupies 1133% of the PADI. The TMRC is based upon current tolerance levels and an assumption that 100% of the sites are treated. Actual exposure levels are likely to be much lower. When the required data are submitted, the Agency will conduct a full tolerance reassessment.

4. SUMMARY OF REGULATORY POSITIONS AND RATIONALES

- * No referral to Special Review is being made at this time.
- * No new tolerances for raw agricultural commodities or significant new uses will be granted until the Agency has received data sufficient to perform a tolerance reassessment. Significant new uses will not be granted until the data gaps have been filled.
- * The Agency is concerned about the potential hazards to aquatic organisms. However, no regulatory action is being considered at this time for fish and wildlife concerns. EPA will reassess the impacts of malathion use on nontarget organisms after the required environmental fate and ecological effects data have been received and reviewed.
- * The Office of Endangered Species (OES) in the U.S. Fish and Wildlife Service has determined that certain uses of malathion may jeopardize the continued existence of endangered species or critical habitat of certain endangered species. No additional labeling is required at this time; however, EPA is developing a program to reduce or eliminate exposure to these species, and may require labeling revisions when the program is developed.
- * In order to meet the statutory standard for continued registration, the Agency has determined that malathion products must bear revised and updated fish and wildlife toxicity warnings.
- * The Agency is deferring decisions concerning malathion's potential for contamination of groundwater until the environmental fate data have been submitted and reviewed.
- * The Agency is not restricting the use of malathion products for retail sale only to certified applicators. Malathion does not meet any of the criteria of 40 CFR 162.11 and therefore products containing malathion do not warrant restricted use classification.
- * The Agency is not establishing a longer reentry interval for agricultural uses of malathion beyond the minimum reentry interval for all agricultural uses of pesticides (sprays have dried, dusts have settled and vapors have dispersed). The Agency will reassess the need for reentry data/reentry intervals upon receipt of the required toxicology data.



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5. SUMMARY OF OUTSTANDING DATA REQUIREMENTSToxicologyTime Frame

Delayed neurotoxicity	9 mos.
21-day dermal toxicity	9 "
90-day inhalation - rat	15 "
Chronic toxicity (rodent and non-rodent)-- using malathion)	50 "
Chronic toxicity (rodent)--using malaoxon	50 "
Oncogenicity (mouse)--using malathion	50 "
Oncogenicity (rat)--using malaoxon	15 "
Teratogenicity - rat	39 "
Reproductive effects - rat (2-generation)	9-12 mos
Mutagenicity	24 mos
Metabolism	15 "
Domestic animal safety testing	

Environmental Fate/Exposure

Hydrolysis	9 mos
Aerobic and anaerobic soil metabolism	27 "
Aerobic and anaerobic aquatic metabolism	27 "
Leaching and adsorption/desorption	12 "
Terrestrial field dissipation	27 "
Long-term field dissipation	50 "
Forestry dissipation	27 "
Aquatic (sediment) - field study	27 "
Photodegradation in water, soil, air	9 "
Volatility (lab)	12 "
Rotational crops (confined)	39 "
Accumulation in irrigated crops	39 "
Accumulation in fish	12 "
Accumulation in aquatic nontarget organisms	12 "
Spray drift	18 "

Residue Chemistry

Storage stability data	18 mos
Plant and animal metabolism	18 "
Residue data - raw agricultural commodities	18 "
Processing studies	24 "
Residue data on stored, unfinished tobacco	18 "
Residues in water	15 "
Residue data on food handling establishments	12 "

Product ChemistryTime Frame

All

9-15 mos

Fish and Wildlife

Acute toxicity to freshwater invertebrates	9 mos
Acute toxicity to estuarine and marine organisms	12 "
Avian reproduction	24 "
Fish early life stage	15 "
Aquatic invertebrate life cycle	15 "
Honeybee - toxicity of residues on foliage	15 "

6. CONTACT PERSON AT EPA

William H. Miller
 Product Manager (16)
 Insecticide-Rodenticide Branch
 Registration Division (TS-767C)
 Office of Pesticide Programs
 Environmental Protection Agency
 401 M Street, SW.
 Washington, DC 20460

Office location and telephone number:
 Rm. 211, Crystal Mall #2
 1921 Jefferson Davis Highway
 Arlington, VA

(703) 557-2600

DISCLAIMER: The information presented in this Chemical Information Fact Sheet is for informational purposes only and may not be used to fulfill data requirements for pesticide registration and reregistration.

WORLD NEWS TONIGHT
"SAFETY ON LAWN PESTICIDES"

9/24/91



A warning to Congress today about the safety of lawn chemicals. More than 70 million home owners use lawn chemicals to kill weeds and bugs and a senate subcommittee was told today that some of them harm the environment and some of the people who use them and their neighbors. Here's ABC's Bill Greenwood.

Tom Latimer wanted his lawn to be a showcase and hired a company that used diazanon, a popular chemical that kills pesky bugs and weeds, but the toxic fumes he inhaled while cutting the grass almost killed him. Tom is brain damaged and 80% disabled. He says his four year old knows something is wrong.

_____ be able to run or swim or take her to the park.

Tom Latimer was one of several witnesses who told senators one-third of the most widely used pesticides can cause brain damage and cancer among people who are particularly sensitive to the chemicals. Toxicologist, Jeanette Sherman, said the protection of people should be put ahead of plants.

To my knowledge nobody has died of weeds.

Three years ago the Federal Environmental Protection Agency began studying the potential danger from 32 widely used lawn

chemicals but not a single report is near completion, so there is no governmental evidence to support a ban. Congress is considering a requirement that neighbors be warned before chemicals are sprayed. The Environmental Protection Agency says even that idea need to be studied.

Bill Greenwood, ABC News, Washington.

That's our report on World News Tonight, I'm Peter Jennings.

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CONFIDENTIAL

American Cyanamid Company
Chemicals Group
One Cyanamid Plaza
Wayne, NJ 07470

March 4, 1991

Ms. Ann C. Levy, Director
Technology Services
Tech Source Development Corporation
NCNB Building, Suite 221
111 University Drive East
College Station, TX 77840

MAR 08 1991

Re: Organophosphorus Degradation Technology

Dear Ms. Levy:

Your letter of February 22nd to Dr. Terenzi has been forwarded to me. The organophosphorus degradation technology is of interest, particularly to our plant in Linden, NJ.

The Linden plant produces Malathion; wastewaters from this process, which contain trace levels of Malathion are treated at a local sewage treatment plant. Recent tests on their discharge suggest that the aerobic treatment may not be adequately removing the Malathion. Do you have specific data on your process relative to detoxification of Malathion? How can this be applied to our discharge to the sewage authority? What testing can be undertaken to demonstrate the applicability of your technology to this issue?

Over the 75 year history of the Linden, NJ plant, several organophosphorus pesticides including: ABATE, COUNTER, THIMET, CYOLANE, CYTROLANE and FAMPHUR as well as Malathion were produced. Also, the plant produced mono - and di-thio acid based salts for use as mining reagents and lube oil additives.

It is possible that the on-going soil and groundwater studies may identify contamination with one or more of these. Any additional data with respect to the application of your technology in treating organophosphate contaminated soils or groundwater would therefore be of interest as would your recommendation on future studies.

I look forward to hearing from you.

Very truly yours,

R. B. Tabakin
Manager, Environmental
Remediation

RBT/st
0612w

cc: J. F. Terenzi

CRAP.

Consumer Products Division

Bioremediation

Mr. D. R. Eger, President
 Tech Source
 Development Corporation
 1111 Bagby, Suite 2610
 Houston, Tx 77002

CONFIDENTIAL



Dear Doug:

As a follow-up to our conversation on May 22, 1991, and the letter I received from Dr. Wild dated May 10, 1991, we are very interested in the concept of bioremediation and the opportunities that this technology can offer the homeowner. The basic research that Drs. Wild and Raushel at Texas A & M have done demonstrates that enzymes can detoxify certain organophosphate insecticides. From our standpoint, we would be interested in supporting a basic research program to develop an enzyme-based system that could be used to detoxify ORTHENE.

I have discussed this program with Dr. Oohomogo, and we both agree that the first phase of the program would be to jointly prepare the protocol for developing and evaluating the enzyme in the laboratory. Specifically, we will want to assist in evaluating the performance of the O-P enzyme in contact with formulated ORTHENE products. It will also be necessary to evaluate the activity of the O-P hydrolase enzyme in the presence of different solvents and surfactant systems typically used in our formulations. We will also need to develop the protocol for evaluating how the enzyme will perform when applied to treated turf and ornamental plants. Subsequent phases of the concept's final development into a marketable product can only be initiated after conducting Market Research to help determine the requirements of the final product.

The Consumer Products Division is willing to fund the first phase of this Research in the amount of \$10,000 over the next 12-18 months. We would request that Texas A & M grant us the exclusive rights to market the enzyme to the consumer for a given period of time to be determined after the development is further defined.

I would appreciate it if you could review this proposal with the appropriate personnel at Texas A & M and advise if it is agreeable to proceed.

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GROUP 180

Sincerely,

J. L. Coltharp
 Product Development
 Coordinator

cc: Mr. M. Garbett
 Mr. C. R. Nelson
 Mr. M. Oohomogo

Chemical weapons incineration years behind schedule

By KEITH SCHNEIDER
New York Times

RICHMOND, Ky. — Hampered by flaws in design and operation, the Army's program to incinerate the nation's enormous stockpile of chemical weapons is falling years behind schedule, experiencing huge cost increases and stirring public protests in six states and the South Pacific.

Using in equal measures the new technological know-how, the Army and the public trust, the Army's Chemical Demilitarization Program is one of the most extraordinarily complex and expensive projects the United States has undertaken to dispose of the wastes and destroy the deadly weapons of the Cold War.

The project is part of the more than \$200 billion the Pentagon has proposed to spend in the next 30 to 50 years to prevent the spread of poison and clean up its contaminated bases and munitions factories.

An even larger project to contain radioactive and toxic wastes at nuclear weapons plants is being managed by the Energy Department. Altogether the government is spending nearly \$6 billion this fiscal year on military environmental projects.

Driven by congressional mandates and a chemical arms treaty President Bush signed with Soviet Mikhail S. Gorbachev, the Soviet Union last June, the Army has proposed burning all its mustard gas stockpile by 1994. The directive was part of an agreement under which Congress allowed the Pentagon to produce a new generation of chemical weapons, the first built since the late 1960s.

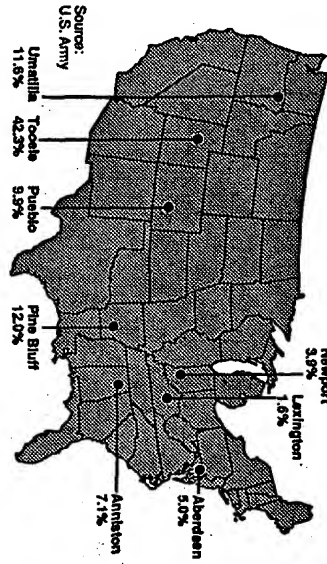
The Army said in 1985 that the incineration technology was well proven and it estimated the cost of the program at \$1.7 billion. In 1988, after the Army acknowledged trouble at its experimental incinerator in Utah, Congress amended the law and extended the deadline until 1997. The cost estimate then climbed to \$3 billion.

Auditors with the General Accounting Office, an investigative arm of Congress, now say the Army may not be finished before 2002, the deadline in the Soviet treaty. In addition, costs have soared to more than \$4 billion.

The Army has spent \$1.2 billion on the program since 1986 and in some respects it has biased new engineering and political paths for Pentagon environmental projects, said Charles

Deadly stockpiles

The Army has proposed burning its stockpiles of nerve and mustard gases in incinerators at nine bases, eight of them in the continental United States. Figures shown are the percentage of the total stockpile at each base; the ninth, with 6.6 percent, is on Johnston Atoll in the South Pacific.



New York Times

Baronian, the deputy program manager. More than \$133 million was used to try to prove the technology in a small incinerator at the Tule Lake Army Depot, 30 miles southwest of Salt Lake City. A larger \$240 million prototype incinerator was constructed on Johnston Atoll.

The Army spent \$182 million building a small advanced incinerator and safely destroying 82, a half-ton, at the Pine Bluff Arsenal, 30 miles southeast of Little Rock, Ark. Last summer, despite opposition in Europe, the United States and the South Pacific, the Army spent \$33 million moving more than 400 tons of chemical arms from U.S. bases in Germany to Johnston Atoll without incident.

The Army has also spent more than \$40 million studying the safety of incineration, considering alternatives, conducting environmental studies, holding innumerable public hearings and financing community groups to review the Army's conduct.

The Army has bent over backwards to be sympathetic to the concerns of citizens," said Baronian from the project's headquarters at the Aberdeen Proving Ground.

In Utah and Alabama, citizens say they are satisfied with how the Army conducted itself and have responded to proposed chemical weapons incinerators with overwhelming support. Not surprisingly, the Army's first \$239 million full-scale incinerator is

under construction at Tule Lake, and a second is nearing final stages of design at the army depot near Aniston.

But in the six other states, and in the island nations of the South Pacific, the Army's proposal to burn its collection of rockets, land mines, projectiles and bombs filled with chemical warfare agents has caused communities to react with disgust and horror.

In one recent protest, 1,000 residents of Madison County, Ky., jammed a school gymnasium to confront Army officials who want to build a \$250 million incinerator to destroy thousands of rockets that are stored at the 15,000-acre Lexington-Blue Grass depot.

"It is just hard for us to believe that this safe little community is where chemical weapons will be burned," said Faye Lakes, the 46-year-old manager of a grocery store in Speedwell, on the southeast boundary of the depot and less than three miles downriver from the proposed incinerator site.

Opal Gentry, Faye's 70-year-old mother and the store's owner, added: "People are going to keep it out. Mind you, we will."

When the Army announced more than six years ago that it intended to incinerate the weapons, it was seen as a threat to a way of life; the reaction was so striking that some residents said even they were surprised. The anger has not lessened at all.

In the last two weeks, the City



New York Times

The Lexington-Blue Grass Army depot in Richmond and Berea, 12 miles south of here, have unanimously passed resolutions urging the Army to halt its program. The Madison County Fiscal Court, the county governing body, also passed a resolution protesting the incinerator, as did the faculty of Berea College, the student senate at Eastern Kentucky University in Richmond and a host of other organizations.

"You ever find anybody who does trust their government?" asked Roscoe V. Buckland, an 81-year-old retired professor of education who lives in Berea. "The Army's gotten the idea they can just push people around out here. You know this is Daniel Boone country. People aren't going to be pushed around."

The Army has never been popular in Madison County. There is still great resentment about the seizure in World War II of the county's best farmland to establish the depot. People became angrier in the 1970s when they learned that the military had filled 49 of the 801 concrete storage bunkers at the depot with obsolete M-55 rockets containing chemicals so dangerous that a tiny drop on the skin or absorbed through the eyes is lethal.

The evidence of potential problems is overwhelming, opponents say. The Army's own studies reported problems at the new incinerator on Johnston Atoll.

At one point, the incinerator leaked trace amounts of chemicals into the air. The Army said it was not a problem, but the residents of the area are not convinced.

"They say it will only take a year and a half to burn rockets out there," said Katherine Flood, a retired bank executive from Richmond. "You can bet they have other plans for a \$250 million incinerator they've only used

tests, the incinerator failed to function 80 percent of the time. Designed to incinerate 192 rockets a day, the equipment was capable of destroying fewer than 50 on the days it operated. Conveyor belts melted, the incinerator overheated and automatic equipment broke down.

Baronian, the deputy program manager, said the Army is spending nearly \$4 million to change equipment at Johnston Atoll, and that subsequent tests have shown better performance.

Peter Hille, an instructor at Berea College, said central Kentucky residents are worried about the release of dioxin, furans and other cancer-causing chemicals. "There isn't an incinerator in the world that has performed anywhere close to what this one has to, to be safe," he said. "There isn't any room for error."

Other opponents said they fear that once the stockpile was burned, that would not be the end of it. The incinerator would continue to be used, they fear, for destroying other toxic military wastes or even for commercial hazardous waste.

"They say it will only take a year and a half to burn rockets out there," said Katherine Flood, a retired bank executive from Richmond. "You can bet they have other plans for a \$250 million incinerator they've only used

**ORTHO****Chevron Chemical Company**

8001 Bollinger Canyon Road, San Ramon, California
Mail Address: P.O. Box 5047, San Ramon, CA 94583-0947 • Fax 510-842-1501

EXHIBIT

M

Consumer Products Division

Sept mb r 20, 1991

CONFIDENTIAL

Ms. A.C. Levy
Director
Technology Services
TechSource Development
Corporation
NCNB Building, Suite 221
111 University Drive East
College Station, TX 77840



Dear Ann:

This will advise that the Consumer Products Division of Chevron Chemical Company is very interested in supporting the initial development phase for the organophosphorus degradation enzyme for Orthene insecticide.

We have prepared a draft agreement indicating our support to be \$25,000 for the first phase of the project. If the research and development is successful, our intent will be to obtain an exclusive license from TechSource to develop and use products from this technology that can be utilized by the consumer.

Sincerely,

J. L. Coltharp
Product Development
Coordinator

cc: M. Garbett

NOV 7 1991

GROUP 180